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<b>(21) International Application Number:</b> PCT/DK99/00260 <b>(22) International Filing Date:</b> 10 May 1999 (10.05.99)  <b>(30) Priority Data:</b> 0636/98 11 May 1998 (11.05.98) DK PA 1998 00875 1 July 1998 (01.07.98) DK  <b>(71) Applicant:</b> NOVO NORDISK A/S [DK/DK]; Novo Allé, DK-2880 Bagsvaerd (DK).  <b>(72) Inventors:</b> HANSEN, Thomas, Kruse; 78 Tibbevangen, DK-2730 Herlev (DK). ANKERSEN, Michael; 34, 1.th Dalgas Have, DK-2000 Frederiksberg (DK).		<b>(81) Designated States:</b> AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, UZ, VN, YU, ZA, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SL, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).  <b>Published</b> <i>With international search report.</i>
<b>(54) Title:</b> COMPOUNDS WITH GROWTH HORMONE RELEASING PROPERTIES  <b>(57) Abstract</b>  The present invention relates to novel compounds, in particular 4,4-disubstituted and 3,3-disubstituted piperidine compounds, compositions containing them, and their use for treating medical disorders resulting from a deficiency in growth hormone.		

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## COMPOUNDS WITH GROWTH HORMONE RELEASING PROPERTIES

## 5 FIELD OF INVENTION

The present invention relates to novel compounds, in particular 4,4-disubstituted and 3,3-disubstituted piperidine compounds, compositions containing them, and their use for treating medical disorders resulting from a deficiency in growth hormone.

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## BACKGROUND OF THE INVENTION

Growth hormone is a hormone which stimulates growth of all tissues capable of growing. In addition, growth hormone is known to have a number of effects on metabolic processes, e.g., stimulation of protein synthesis and free fatty acid mobilisation and to cause a switch in energy metabolism from carbohydrate to fatty acid metabolism. Deficiency in growth hormone can result in a number of severe medical disorders, e.g., dwarfism.

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Growth hormone is released from the pituitary. The release is under tight control of a number of hormones and neurotransmitters either directly or indirectly. Growth hormone release can be stimulated by growth hormone releasing hormone (GHRH) and inhibited by somatostatin. In both cases the hormones are released from the hypothalamus but their action is mediated primarily via specific receptors located in the pituitary. Other compounds which stimulate the release of growth hormone from the pituitary have also been described. For example arginine, L-3,4-dihydroxyphenylalanine (L-Dopa), glucagon, vasopressin, PACAP (pituitary adenylyl cyclase activating peptide), muscarinic receptor agonists and a synthetic hexapeptide, GHRP (growth hormone releasing peptide) release endogenous growth hormone either by a direct effect on the pituitary or by affecting the release of GHRH and/or somatostatin from the hypothalamus.

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In disorders or conditions where increased levels of growth hormone is desired, the protein nature of growth hormone makes anything but parenteral administration non-viable.

Furthermore, other directly acting natural secretagogues, e.g., GHRH and PACAP, are longer polypeptides for which reason parenteral administration is preferred.

The use of certain compounds for increasing the levels of growth hormone in mammals has previously been proposed, e.g. in EP 18 072, EP 83 864, WO 89/07110, WO 89/01711, WO 89/10933, WO 88/9780, WO 83/02272, WO 91/18016, WO 92/01711, WO 93/04081, WO 9517422, WO 9517423, WO 9514666, WO9419367, WO9534311, WO9602530, WO9615148, WO9613265, WO9622997, WO9635713, WO9638471, WO9632943, WO9700894, WO9706803, WO9709060, WO9707117, WO9711697, WO9722620, WO9723508, WO9724369, and WO9734604.

The composition of growth hormone releasing compounds is important for their growth hormone releasing potency as well as their bioavailability. It is therefore an object of the present invention to provide novel compounds with growth hormone releasing properties. Moreover, it is an object to provide novel growth hormone releasing compounds (growth hormone secretagogues) which are specific and/or selective and have no or substantially no side-effects, such as e.g. release of LH, FSH, TSH, ACTH, vasopressin, oxytocin, cortisol and/or prolactin. It is also an object to provide compounds which have good oral bioavailability.

## SUMMARY OF THE INVENTION

In accordance with the present invention there is provided novel compounds which act directly on the pituitary cells under normal experimental conditions in vitro to release growth hormone therefrom.

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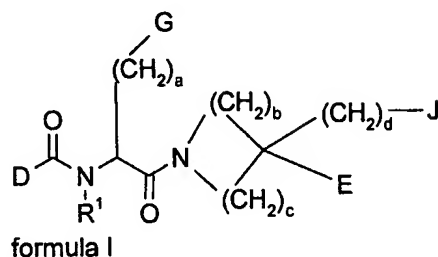
These growth hormone releasing compounds can be utilized in vitro as unique research tools for understanding, inter alia, how growth hormone secretion is regulated at the pituitary level.

Moreover, the growth hormone releasing compounds of the present invention can also be administered in vivo to increase endogenous growth hormone release.

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## DESCRIPTION OF THE INVENTION

Accordingly, in a broad aspect the present invention relates to a compound of general formula I



wherein

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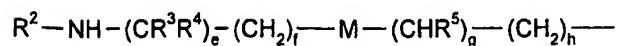
R<sup>1</sup> is hydrogen, or C<sub>1-6</sub>-alkyl optionally substituted with one or more aryl or hetaryl;

a and d are independently of each other 0, 1, 2 or 3;

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b and c are independently of each other 0, 1, 2, 3, 4 or 5, provided that b + c is 3, 4 or 5,

D is



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wherein R<sup>2</sup>, R<sup>3</sup>, R<sup>4</sup> and R<sup>5</sup> are independently hydrogen or C<sub>1-6</sub> alkyl optionally substituted with one or more halogen, amino, hydroxyl, aryl or hetaryl; or

R<sup>2</sup> and R<sup>3</sup> or R<sup>2</sup> and R<sup>4</sup> or R<sup>3</sup> and R<sup>4</sup> may optionally form -(CH<sub>2</sub>)<sub>i</sub>-U-(CH<sub>2</sub>)<sub>j</sub>-, wherein i and j are independently 1 or 2 and U is -O-, -S- or a valence bond;

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h and f are independently 0, 1, 2, or 3;

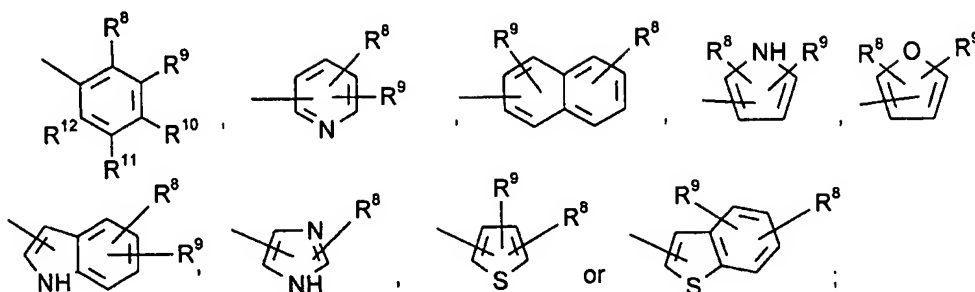
g and e are independently 0 or 1;

M is a valence bond, -CR<sup>6</sup>=CR<sup>7</sup>-, arylene, hetarylene, -O- or -S-;

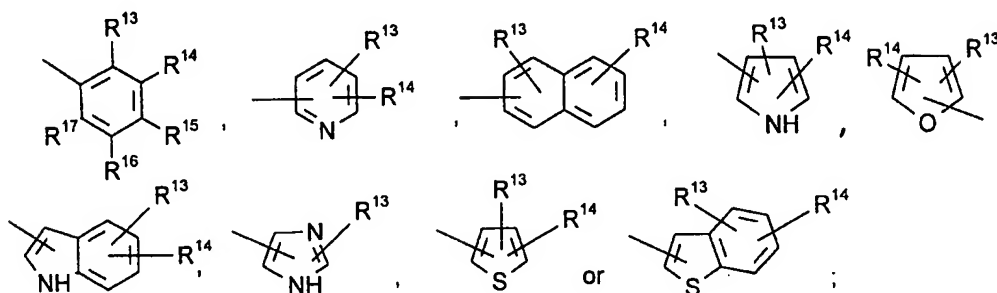
R<sup>6</sup> and R<sup>7</sup> are independently hydrogen, or C<sub>1-6</sub>-alkyl optionally substituted with one or more aryl or hetaryl;

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G is  $-\text{O}-(\text{CH}_2)_k-\text{R}^8$ ,



5 J is  $-\text{O}-(\text{CH}_2)_l-\text{R}^{13}$ ,



wherein  $\text{R}^8$ ,  $\text{R}^9$ ,  $\text{R}^{10}$ ,  $\text{R}^{11}$ ,  $\text{R}^{12}$ ,  $\text{R}^{13}$ ,  $\text{R}^{14}$ ,  $\text{R}^{15}$ ,  $\text{R}^{16}$  and  $\text{R}^{17}$  independently of each other are  
 10 hydrogen, halogen, aryl, hetaryl,  $\text{C}_{1-6}$ -alkyl or  $\text{C}_{1-6}$ -alkoxy;  
 k and l are independently 0, 1 or 2;

E is  $-\text{CONR}^{18}\text{R}^{19}$ ,  $-\text{COOR}^{19}$ ,  $-(\text{CH}_2)_m-\text{NR}^{18}\text{SO}_2\text{R}^{20}$ ,  $-(\text{CH}_2)_m-\text{NR}^{18}\text{COR}^{20}$ ,  $-(\text{CH}_2)_m-\text{OR}^{19}$ ,  
 $-(\text{CH}_2)_m-\text{OCOR}^{20}$ ,  $-\text{CH}(\text{R}^{16})\text{R}^{19}$ ,  $-(\text{CH}_2)_m-\text{NR}^{18}-\text{CS}-\text{NR}^{19}\text{R}^{21}$  or  
 15  $-(\text{CH}_2)_m-\text{NR}^{18}-\text{CO}-\text{NR}^{19}\text{R}^{21}$ ; or

E is  $-\text{CONR}^{22}\text{NR}^{23}\text{R}^{24}$ , wherein  $\text{R}^{22}$  is hydrogen,  $\text{C}_{1-6}$ -alkyl optionally substituted with one or  
 more aryl or hetaryl, or aryl or hetaryl optionally substituted with one or more  $\text{C}_{1-6}$ -alkyl;  $\text{R}^{23}$  is  
 $\text{C}_{1-6}$ -alkyl optionally substituted with one or more aryl or hetaryl, or  $\text{C}_{1-7}$ -acyl; and  $\text{R}^{24}$  is  
 20 hydrogen,  $\text{C}_{1-6}$ -alkyl optionally substituted with one or more aryl or hetaryl; or aryl or hetaryl  
 optionally substituted with one or more  $\text{C}_{1-6}$ -alkyl; or

$R^{22}$  and  $R^{23}$  together with the nitrogen atoms to which they are attached may form a heterocyclic system optionally substituted with one or more  $C_{1-6}$ -alkyl, halogen, amino, hydroxyl, aryl or hetaryl; or

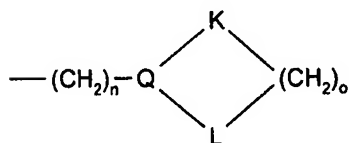
- 5  $R^{22}$  and  $R^{24}$  together with the nitrogen atoms to which they are attached may form a heterocyclic system optionally substituted with one or more  $C_{1-6}$ -alkyl, halogen, amino, hydroxyl, aryl or hetaryl; or

- $R^{23}$  and  $R^{24}$  together with the nitrogen atom to which they are attached may form a heterocyclic system optionally substituted with one or more  $C_{1-6}$ -alkyl, halogen, amino, hydroxyl, aryl or hetaryl;
- 10

wherein m is 0, 1, 2 or 3,

- $R^{18}$ ,  $R^{19}$  and  $R^{21}$  independently are hydrogen or  $C_{1-6}$ -alkyl optionally substituted with halogen, -
- 15  $N(R^{25})R^{26}$ , wherein  $R^{25}$  and  $R^{26}$  are independently hydrogen or  $C_{1-6}$  alkyl; hydroxyl,  $C_{1-6}$ -alkoxy,  $C_{1-6}$ -alkoxycarbonyl,  $C_{1-6}$ -alkylcarbonyloxy or aryl;

or  $R^{19}$  is



wherein

Q is  $-CH<$  or  $-N<$ ,

K and L are independently  $-CH_2-$ ,  $-CO-$ ,  $-O-$ ,  $-S-$ ,  $-NR^{27}-$  or a valence bond,

where  $R^{27}$  is hydrogen or  $C_{1-6}$  alkyl;

- 25 n and o are independently 0, 1, 2, 3 or 4;

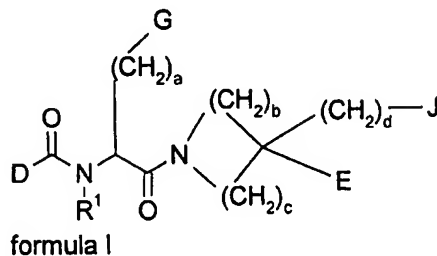
$R^{20}$  is  $C_{1-6}$  alkyl, aryl or hetaryl;

or a pharmaceutically acceptable salt thereof;

with the proviso that

if M is a valence bond then E is  $-CONR^{22}NR^{23}R^{24}$ .

In a more narrow aspect the present invention relates to a compound of the general formula I



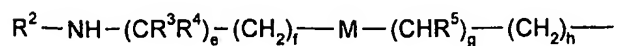
wherein

R<sup>1</sup> is hydrogen, or C<sub>1-6</sub>-alkyl optionally substituted with one or more aryl or hetaryl;

a and d are independently of each other 0, 1, 2 or 3;

b and c are independently of each other 0, 1, 2, 3, 4 or 5, provided that b + c is 3, 4 or 5,

D is



wherein R<sup>2</sup>, R<sup>3</sup>, R<sup>4</sup> and R<sup>5</sup> are independently hydrogen or C<sub>1-6</sub> alkyl optionally substituted with one or more halogen, amino, hydroxyl, aryl or hetaryl; or

R<sup>2</sup> and R<sup>3</sup> or R<sup>2</sup> and R<sup>4</sup> or R<sup>3</sup> and R<sup>4</sup> may optionally form -(CH<sub>2</sub>)<sub>i</sub>-U-(CH<sub>2</sub>)<sub>j</sub>-, wherein i and j are independently 1 or 2 and U is -O-, -S- or a valence bond;

h and f are independently 0, 1, 2, or 3;

g and e are independently 0 or 1;

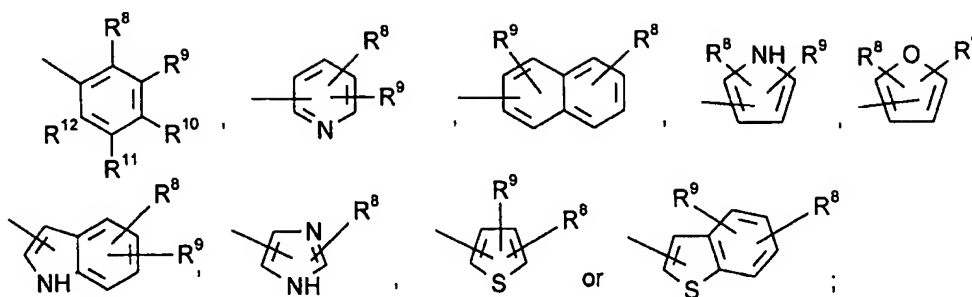
M is -CR<sup>6</sup>=CR<sup>7</sup>-, arylene, hetarylene, -O- or -S-;

R<sup>6</sup> and R<sup>7</sup> are independently hydrogen, or C<sub>1-6</sub>-alkyl optionally substituted with one or more aryl or hetaryl;

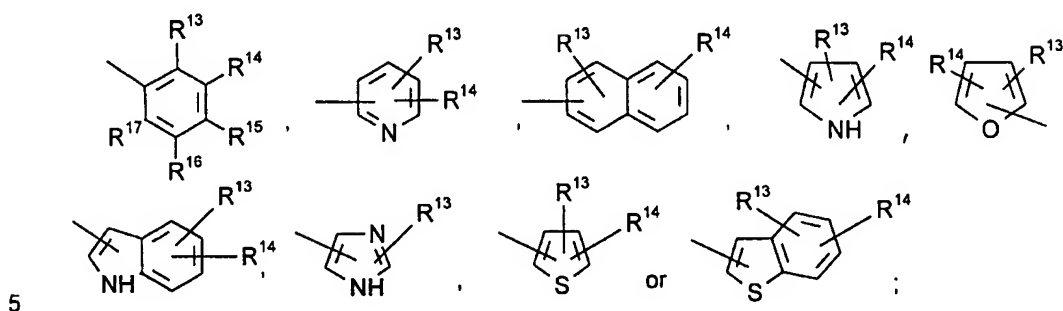
G is -O-(CH<sub>2</sub>)<sub>k</sub>-R<sup>8</sup>,



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J is  $-O-(CH_2)_r-R^{13}$ ,



wherein  $R^8, R^9, R^{10}, R^{11}, R^{12}, R^{13}, R^{14}, R^{15}, R^{16}$  and  $R^{17}$  independently of each other are hydrogen, halogen, aryl, hetaryl,  $C_{1-6}$ -alkyl or  $C_{1-6}$ -alkoxy;

k and l are independently 0, 1 or 2;

E is  $-\text{CONR}^{18}\text{R}^{19}$ ,  $-\text{COOR}^{19}$ ,  $-(\text{CH}_2)_m-\text{NR}^{18}\text{SO}_2\text{R}^{20}$ ,  $-(\text{CH}_2)_m-\text{NR}^{18}\text{COR}^{20}$ ,  $-(\text{CH}_2)_m-\text{OR}^{19}$ ,  $-(\text{CH}_2)_m-\text{OCOR}^{20}$ ,  $-\text{CH}(\text{R}^{18})\text{R}^{19}$ ,  $-(\text{CH}_2)_m-\text{NR}^{18}-\text{CS}-\text{NR}^{19}\text{R}^{21}$  or  $-(\text{CH}_2)_m-\text{NR}^{18}-\text{CO}-\text{NR}^{19}\text{R}^{21}$ ; or

E is  $-\text{CONR}^{22}\text{NR}^{23}\text{R}^{24}$ , wherein  $R^{22}$  is hydrogen,  $C_{1-6}$ -alkyl optionally substituted with one or more aryl or hetaryl, or aryl or hetaryl optionally substituted with one or more  $C_{1-6}$ -alkyl;  $R^{23}$  is  $C_{1-6}$ -alkyl optionally substituted with one or more aryl or hetaryl, or  $C_{1-7}$ -acyl; and  $R^{24}$  is hydrogen,  $C_{1-6}$ -alkyl optionally substituted with one or more aryl or hetaryl; or aryl or hetaryl optionally substituted with one or more  $C_{1-6}$ -alkyl; or

R<sup>22</sup> and R<sup>23</sup> together with the nitrogen atoms to which they are attached may form a heterocyclic system optionally substituted with one or more C<sub>1-6</sub>-alkyl, halogen, amino, hydroxyl, aryl or hetaryl; or

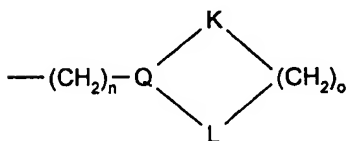
- 5 R<sup>22</sup> and R<sup>24</sup> together with the nitrogen atoms to which they are attached may form a heterocyclic system optionally substituted with one or more C<sub>1-6</sub>-alkyl, halogen, amino, hydroxyl, aryl or hetaryl; or

- 10 R<sup>23</sup> and R<sup>24</sup> together with the nitrogen atom to which they are attached may form a heterocyclic system optionally substituted with one or more C<sub>1-6</sub>-alkyl, halogen, amino, hydroxyl, aryl or hetaryl;

wherein m is 0, 1, 2 or 3,

- R<sup>18</sup>, R<sup>19</sup> and R<sup>21</sup> independently are hydrogen or C<sub>1-6</sub>-alkyl optionally substituted with halogen, -  
 15 N(R<sup>25</sup>)R<sup>26</sup>, wherein R<sup>25</sup> and R<sup>26</sup> are independently hydrogen or C<sub>1-6</sub> alkyl; hydroxyl, C<sub>1-6</sub>-alkoxy, C<sub>1-6</sub>-alkoxycarbonyl, C<sub>1-6</sub>-alkylcarbonyloxy or aryl;

or R<sup>19</sup> is



wherein

Q is -CH< or -N< ,

K and L are independently -CH<sub>2</sub>-, -CO-, -O-, -S-, -NR<sup>27</sup>- or a valence bond,  
 wherein R<sup>27</sup> is hydrogen or C<sub>1-6</sub> alkyl;

- 25 n and o are independently 0, 1, 2, 3 or 4;

R<sup>20</sup> is C<sub>1-6</sub> alkyl, aryl or hetaryl;

or a pharmaceutically acceptable salt thereof.

- Moreover, the compounds of formula I may comprise any optical isomers thereof, in the form  
 30 of separated, pure or partially purified optical isomers or racemic mixtures thereof. Whenever

one or more chiral carbon atoms are present such chiral center or centers may be in the R- and/or S-configuration, or a mixture of R and S.

Furthermore, the compounds of formula I may have one or more carbon-carbon double  
 5 bonds with the possibility of geometric isomeri, and it is intended that possible stereoisomers (E or Z isomers) are included in the scope of the invention, unless a special geometric isomer is specified.

In one embodiment of the compound of formula I R<sup>1</sup> is hydrogen. In another embodiment of  
 10 the compound of formula I R<sup>1</sup> is C<sub>1-6</sub>-alkyl, such as C<sub>1-4</sub>-alkyl, in particular methyl.

In a further embodiment of the compound of formula I a is 1.

In a still further embodiment of the compound of formula I d is 1.

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In a further embodiment of the compound of formula I b is 1.

In a still further embodiment of the compound of formula I b is 2.

In a further embodiment of the compound of formula I b is 3.

20 In a still further embodiment of the compound of formula I c is 1.

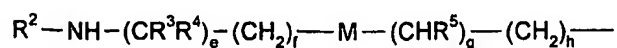
In a further embodiment of the compound of formula I c is 2.

In a still further embodiment of the compound of formula I c is 3.

In a particular embodiment of the compound of formula I b+c is 4.

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In a further embodiment of the compound of formula I D is



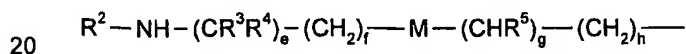
30 wherein R<sup>2</sup>, R<sup>3</sup>, R<sup>4</sup> and R<sup>5</sup> are independently hydrogen or C<sub>1-6</sub> alkyl optionally substituted with one or more halogen, amino, hydroxyl, aryl or hetaryl; or R<sup>2</sup> and R<sup>3</sup> or R<sup>2</sup> and R<sup>4</sup> or R<sup>3</sup> and R<sup>4</sup> may optionally form -(CH<sub>2</sub>)<sub>i</sub>-U-(CH<sub>2</sub>)<sub>j</sub>-, wherein i and j are independently 1 or 2 and U is -O-, -S- or a valence bond,

h and f are independently 0, 1, 2, or 3;

g and e are independently 0 or 1;

- M is  $-\text{CR}^6=\text{CR}^7-$ , arylene, hetarylene,  $-\text{O}-$  or  $-\text{S}-$ ; wherein  $\text{R}^6$  and  $\text{R}^7$  are independently hydrogen, or  $\text{C}_{1-6}$ -alkyl. In one embodiment  $\text{R}^2$  is hydrogen. In a second embodiment  $\text{R}^3$  is hydrogen. In a third embodiment  $\text{R}^3$  is  $\text{C}_{1-6}$  alkyl, in particular methyl. In a further embodiment  $\text{R}^4$  is hydrogen. In a still further embodiment  $\text{R}^4$  is  $\text{C}_{1-6}$  alkyl, in particular methyl. In a further embodiment  $\text{R}^3$  and  $\text{R}^4$  form  $-(\text{CH}_2)_i\text{U}-(\text{CH}_2)_j-$ . In a still further embodiment i is 1. In a further embodiment i is 2. In a still further embodiment j is 1. In a further embodiment j is 2. In a still further embodiment U is a valence bond. In a further embodiment  $\text{R}^3$  and  $\text{R}^4$  form  $-(\text{CH}_2)_3-$ . In a further embodiment h is 0. In a still further embodiment f is 0. In a further embodiment f is 1. In a further embodiment g is 0. In a still further embodiment e is 0. In a further embodiment e is 1. In a still further embodiment M is  $-\text{CR}^6=\text{CR}^7-$ , arylene,  $-\text{O}-$ , or  $-\text{S}-$ . In a further embodiment both of  $\text{R}^6$  and  $\text{R}^7$  are hydrogen or one of  $\text{R}^6$  and  $\text{R}^7$  is methyl and the other is hydrogen. In a still further embodiment M is the E-isomer of  $-\text{CR}^6=\text{CR}^7-$ . In a further embodiment M is  $-\text{CH}=\text{CH}-$ . In a still further embodiment M is  $-\text{C}(\text{CH}_3)=\text{CH}-$ . In a further embodiment M is arylene, in particular phenylene.

In a still further embodiment In a further embodiment of the compound of formula I D is



wherein  $\text{R}^2$ ,  $\text{R}^3$ ,  $\text{R}^4$  and  $\text{R}^5$  are independently hydrogen or  $\text{C}_{1-6}$  alkyl optionally substituted with one or more halogen, amino, hydroxyl, aryl or hetaryl; or

- $\text{R}^2$  and  $\text{R}^3$  or  $\text{R}^2$  and  $\text{R}^4$  or  $\text{R}^3$  and  $\text{R}^4$  may optionally form  $-(\text{CH}_2)_i\text{U}-(\text{CH}_2)_j-$ , wherein i and j are independently 1 or 2 and U is  $-\text{O}-$ ,  $-\text{S}-$  or a valence bond,

h and f are independently 0, 1, 2, or 3;

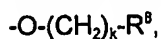
g and e are independently 0 or 1;

- M is a valence bond. In one embodiment  $\text{R}^2$  is hydrogen. In a second embodiment  $\text{R}^3$  is hydrogen. In a third embodiment  $\text{R}^3$  is  $\text{C}_{1-6}$  alkyl, in particular methyl. In a further embodiment  $\text{R}^4$  is hydrogen. In a still further embodiment  $\text{R}^4$  is  $\text{C}_{1-6}$  alkyl, in particular methyl. In a further embodiment  $\text{R}^3$  and  $\text{R}^4$  form  $-(\text{CH}_2)_i\text{U}-(\text{CH}_2)_j-$ . In a still further embodiment i is 1. In a further embodiment i is 2. In a still further embodiment j is 1. In a further embodiment j is 2. In a still further embodiment U is a valence bond. In a further embodiment  $\text{R}^3$  and  $\text{R}^4$  form  $-(\text{CH}_2)_3-$ . In a

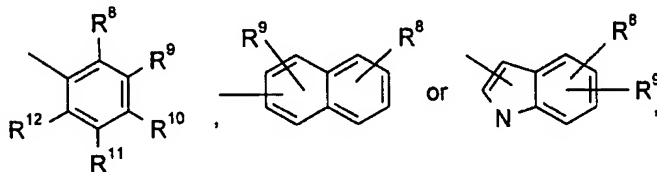
further embodiment h is 0. In a still further embodiment f is 0. In a further embodiment f is 1. In a further embodiment g is 0. In a still further embodiment e is 0. In a further embodiment e is 1. In a preferred embodiment of the compound of formula I D is (1E)-4-amino-4-methylpent-1-enyl,

- 5 (1E)-4-amino-2,4-dimethylpent-1-enyl, (1E)-3-(1-aminocyclobutyl)prop-1-enyl, 1-amino-1-methylethyl, or 3-aminomethylphenyl.

In a still further embodiment of the compound of formula I G is



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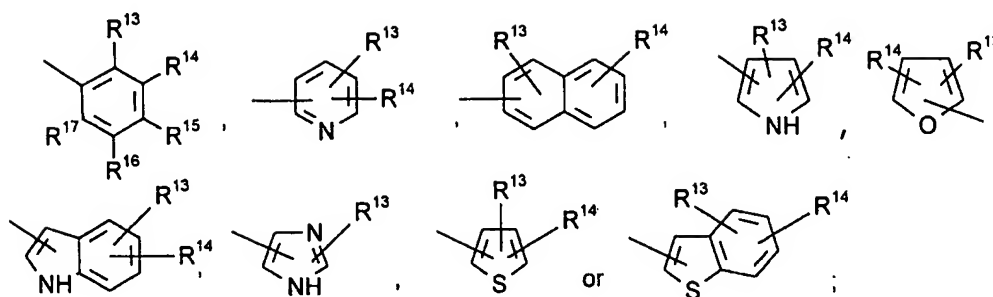


- wherein R<sup>8</sup>, R<sup>9</sup>, R<sup>10</sup>, R<sup>11</sup> and R<sup>12</sup> independently of each other are hydrogen, halogen, aryl, hetaryl, C<sub>1-6</sub>-alkyl or C<sub>1-6</sub>-alkoxy; k is 0, 1 or 2. In a further embodiment R<sup>8</sup>, R<sup>9</sup>, R<sup>10</sup>, R<sup>11</sup> and R<sup>12</sup> are independently of each other hydrogen. In a still further embodiment one of R<sup>8</sup>, R<sup>9</sup>, R<sup>10</sup>, R<sup>11</sup> and R<sup>12</sup> is phenyl and the others are hydrogen, in particular R<sup>10</sup> is phenyl. In a further embodiment R<sup>8</sup> is phenyl. In a still further embodiment k is 1. In a still further embodiment G is phenyl, 1-naphthyl or 2-naphthyl, preferably phenyl or 2-naphthyl. In a further embodiment G is benzyloxy. In a still further embodiment G is 1H-indol. In a further embodiment G is biphenyl-4-yl.
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- 20

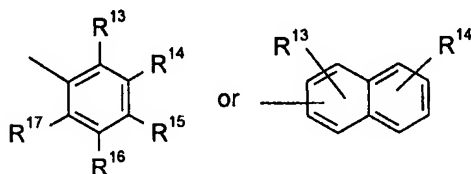
In the above compound of formula I G is preferably 2-naphthyl, benzyloxy, 1H-indol or biphenyl-4-yl.

- 25 In a further embodiment of the compound of formula I J is

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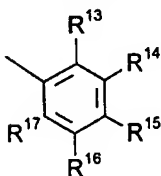


wherein  $R^{13}$ ,  $R^{14}$ ,  $R^{15}$ ,  $R^{16}$  and  $R^{17}$  independently of each other are hydrogen, halogen, aryl, hetaryl,  $C_{1-6}$ -alkyl or  $C_{1-6}$ -alkoxy. In a still further embodiment J is



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In a particular embodiment J is



In a preferred embodiment  $R^{13}$ ,  $R^{14}$ ,  $R^{15}$ ,  $R^{16}$  and  $R^{17}$  are all hydrogen.

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In a still further embodiment of the compound of formula I E is  $-\text{CONR}^{18}\text{R}^{19}$ ,  $-\text{COOR}^{19}$  or  $-(\text{CH}_2)_m-\text{OR}^{19}$ , wherein m is 0, 1, 2 or 3,  $R^{18}$  and  $R^{19}$  independently are hydrogen or  $C_{1-6}$ -alkyl optionally substituted by halogen,  $-\text{N}(\text{R}^{25})\text{R}^{26}$  wherein  $R^{25}$  and  $R^{26}$  are independently hydrogen or  $C_{1-6}$  alkyl; hydroxyl,  $C_{1-6}$ -alkoxy,  $C_{1-6}$ -alkoxycarbonyl,  $C_{1-6}$ -alkylcarbonyloxy or aryl. In a particular embodiment E is  $-\text{CONR}^{18}\text{R}^{19}$ . In a further embodiment  $R^{18}$  and  $R^{19}$  are independently hydrogen or  $C_{1-6}$ -alkyl. In a particular embodiment one of  $R^{18}$  and  $R^{19}$  is hydrogen and the other is methyl. In a further embodiment E is  $-\text{COOR}^{19}$ . In a particular embodiment  $R^{19}$  is  $C_{1-6}$ -alkyl, in particular ethyl.

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In another embodiment E is  $-\text{CONR}^{22}\text{NR}^{23}\text{R}^{24}$ , wherein  $R^{22}$  is hydrogen,  $C_{1-6}$ -alkyl optionally substituted with one or more aryl or hetaryl, or aryl or hetaryl optionally substituted with one or more  $C_{1-6}$ -alkyl;  $R^{23}$  is  $C_{1-6}$ -alkyl optionally substituted with one or more aryl or hetaryl, or  $C_{1-7}$ -

acyl; and R<sup>24</sup> is hydrogen, C<sub>1-6</sub>-alkyl optionally substituted with one or more aryl or hetaryl; or aryl or hetaryl optionally substituted with one or more C<sub>1-6</sub>-alkyl; or

R<sup>22</sup> and R<sup>23</sup> together with the nitrogen atoms to which they are attached may form a heterocyclic system optionally substituted with one or more C<sub>1-6</sub>-alkyl, halogen, amino, hydroxyl, aryl or hetaryl; or

R<sup>22</sup> and R<sup>24</sup> together with the nitrogen atoms to which they are attached may form a heterocyclic system optionally substituted with one or more C<sub>1-6</sub>-alkyl, halogen, amino, hydroxyl, aryl or hetaryl; or

R<sup>23</sup> and R<sup>24</sup> together with the nitrogen atom to which they are attached may form a heterocyclic system optionally substituted with one or more C<sub>1-6</sub>-alkyl, halogen, amino, hydroxyl, aryl or hetaryl. In a still further embodiment R<sup>22</sup> is hydrogen. In another embodiment R<sup>22</sup> is C<sub>1-6</sub>-alkyl, such as C<sub>1-4</sub>-alkyl, in particular methyl. In a further embodiment R<sup>23</sup> is C<sub>1-6</sub>-alkyl, such as C<sub>1-4</sub>-alkyl, in particular methyl. In another embodiment R<sup>23</sup> is C<sub>1-7</sub>-acyl, such as C<sub>2-4</sub>-acyl, in particular acetyl. In a still further embodiment of the compound of formula I R<sup>24</sup> is hydrogen. In another embodiment of the compound of formula I R<sup>24</sup> is C<sub>1-6</sub>-alkyl, such as C<sub>1-4</sub>-alkyl, in particular methyl. In a special embodiment R<sup>22</sup> is hydrogen and R<sup>23</sup> and R<sup>24</sup> are C<sub>1-6</sub>-alkyl, such as C<sub>1-4</sub>-alkyl, in particular methyl. In a further embodiment R<sup>22</sup> and R<sup>23</sup> may together with the nitrogen atoms to which they are attached form a heterocyclic system, which is optionally substituted with one or more C<sub>1-6</sub>-alkyl, halogen, amino, hydroxyl, aryl or hetaryl. Such heterocyclic system, including R<sup>22</sup> and R<sup>23</sup>, may be aromatic or non-aromatic and may be selected from e.g. pyrazole, pyridazine, triazine, indazole, phthalazine, cinnoline, pyrazolidine, or pyrazoline. In a still further embodiment R<sup>22</sup> and R<sup>24</sup> together with the nitrogen atoms to which they are attached form a heterocyclic system, which is optionally substituted with one or more C<sub>1-6</sub>-alkyl, halogen, amino, hydroxyl, aryl or hetaryl. Such heterocyclic system, including R<sup>22</sup> and R<sup>24</sup>, may be aromatic or non-aromatic and may be selected from e.g. pyrazole, pyridazine, triazine, indazole, phthalazine, cinnoline, pyrazolidine, or pyrazoline. In a further embodiment of the compound of formula I R<sup>23</sup> and R<sup>24</sup> together with the nitrogen atom to which they are attached form a heterocyclic system, which is optionally substituted with one or more C<sub>1-6</sub>-alkyl, halogen, amino, hydroxyl, aryl or hetaryl. Such heterocyclic system, including R<sup>22</sup> and R<sup>23</sup>, may be aromatic or non-aromatic and may be selected from e.g. aziridine, dithiazine, pyrrol, imidazol, pyrazole, isoindole, indole, indazole, purine, pyrrolidine, pyrroline, imidazolidine, imidazoline, pyrazolidine, pyrazoline, piperidine, piperazine, indoline, isoindoline, or morpholine. In a

particular embodiment  $R^{23}$  and  $R^{24}$  together with the nitrogen atom to which they are attached form pyrrolidine.

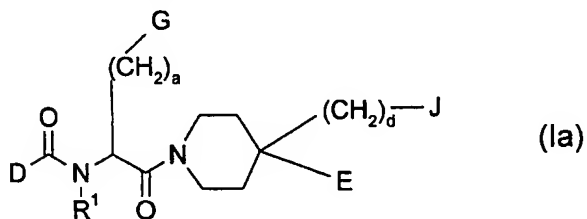
When  $R^{22}$  and  $R^{23}$  form a heterocyclic system  $R^{23}$  and  $R^{24}$  may simultaneously also form a  
 5 heterocyclic system or  $R^{24}$  may be hydrogen,  $C_{1-6}$ -alkyl optionally substituted with one or more aryl or hetaryl, or aryl or hetaryl optionally substituted with one or more  $C_{1-6}$ -alkyl.

When  $R^{22}$  and  $R^{24}$  form a heterocyclic system  $R^{23}$  and  $R^{24}$  may simultaneously also form a  
 10 heterocyclic system or  $R^{23}$  may be  $C_{1-6}$ -alkyl optionally substituted with one or more aryl or hetaryl, or  $C_{1-7}$ -acyl.

In the above compound of formula I E is preferably (methylamino)carbonyl, N,N-dimethylhydrazinocarbonyl, ethoxycarbonyl, or (pyrrolidin-1-yl)aminocarbonyl.

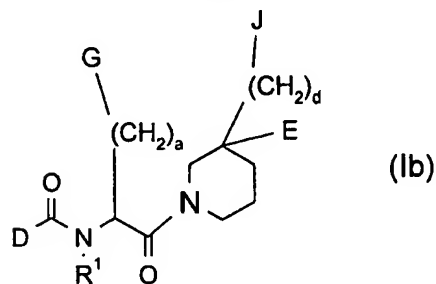
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A particularly preferred group of compounds of formula I are such having formula Ia



wherein  $R^1$ , D, G, E, J, a and d are as defined above.

20 Another particularly preferred group of compounds of formula I are such having formula Ib

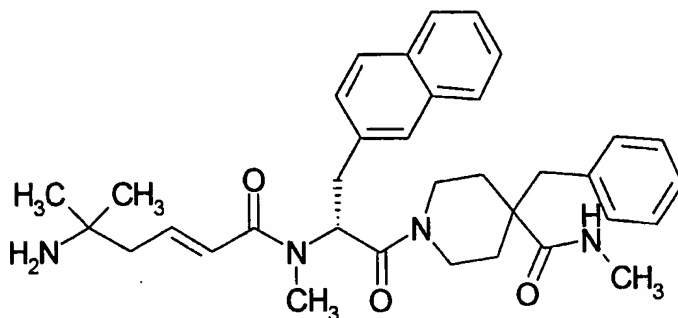


wherein  $R^1$ , D, G, E, J, a and d are as defined above.



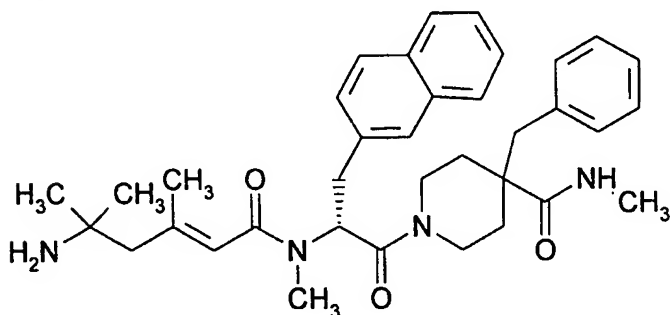
Preferred compounds of formula I of the invention are:

1-((2R)-2-[N-((2E)-5-Amino-5-methylhex-2-enoyl)-N-methylamino]-3-(2-naphthyl)propionyl)-4-benzylpiperidine-4-carboxylic acid methylamide



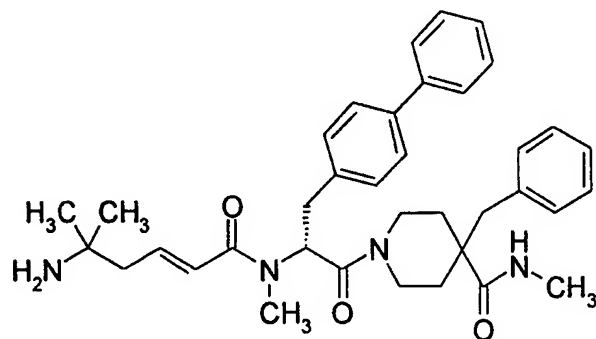
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1-((1R)-2-[N-((2E)-5-Amino-3,5-dimethylhex-2-enoyl)-N-methylamino]-3-(2-naphthyl)propionyl)-4-benzylpiperidine-4-carboxylic acid methylamide



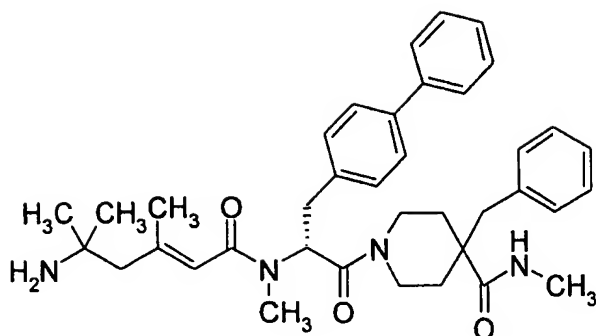
1-((2R)-2-[N-((2E)-5-Amino-5-methylhex-2-enoyl)-N-methylamino]-3-(biphenyl-4-yl)propionyl)-4-benzylpiperidine-4-carboxylic acid methylamide

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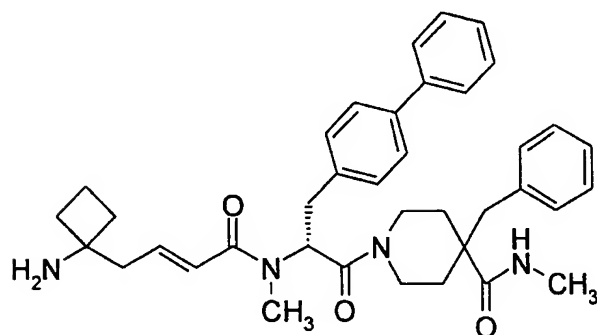


1-((2R)-2-[N-((2E)-5-Amino-3,5-dimethylhex-2-enoyl)-N-methylamino]-3-(biphenyl-4-yl)propionyl)-4-benzylpiperidine-4-carboxylic acid methylamide

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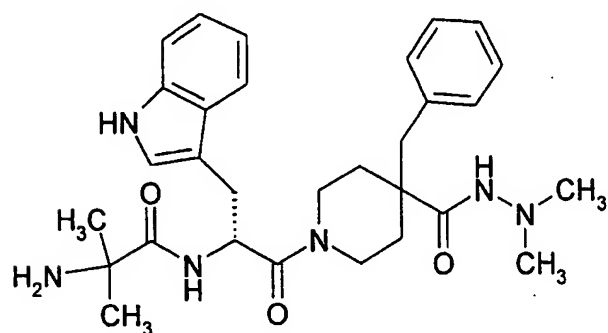


1-((2R)-2-{N-[(2E)-4-(1-Aminocyclobutyl)but-2-enoyl]-N-methylamino}-3-(biphenyl-4-yl)propionyl)-4-benzylpiperidine-4-carboxylic acid methylamide



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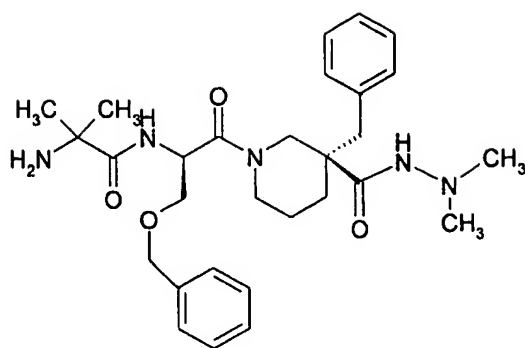
2-Amino-N-[(1R)-2-[4-benzyl-4-(N',N'-dimethylhydrazinocarbonyl)piperidin-1-yl]-1-((1H-indol-3-yl)methyl)-2-oxoethyl]-2-methylpropionamide



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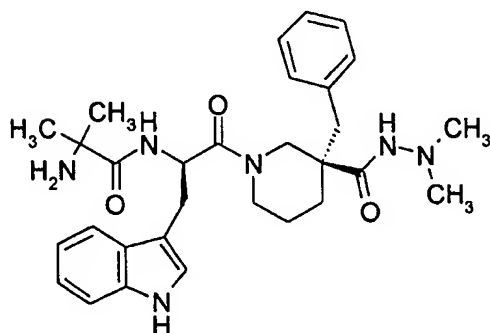
2-Amino-N-[(1R)-2-[(3R)-3-benzyl-3-(N',N'-dimethylhydrazinocarbonyl)piperidin-1-yl]-1-benzylloxymethyl-2-oxoethyl]-2-methylpropionamide

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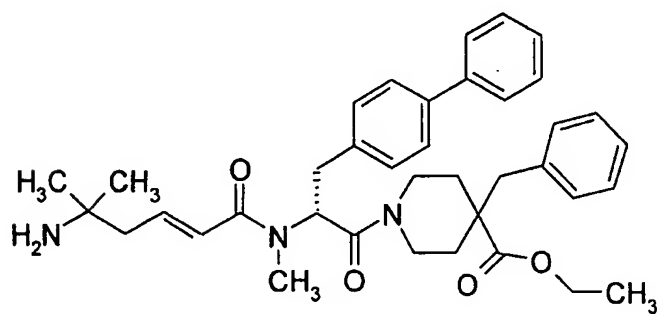
2-Amino-N-[(1R)-2-[(3R)-3-benzyl-3-(N,N'-dimethylhydrazinocarbonyl)-piperidin-1-yl]-1-((1H-indol-3-yl)methyl)-2-oxoethyl]-2-methylpropionamide

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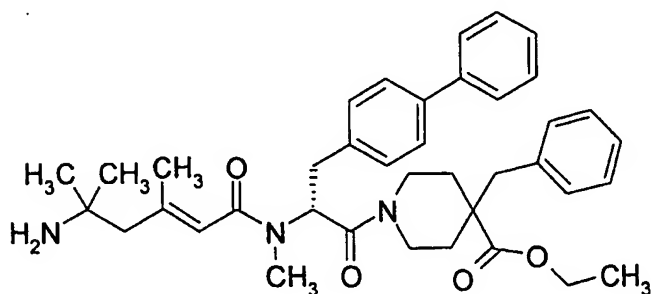
1-((2R)-2-[N-((2E)-5-Amino-5-methylhex-2-enoyl)-N-methylamino]-3-(biphenyl-4-yl)propionyl)-4-benzylpiperidine-4-carboxylic acid ethyl ester

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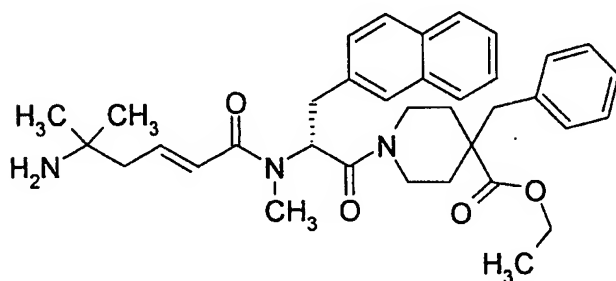
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1-((2R)-2-[N-((2E)-5-Amino-3,5-dimethylhex-2-enoyl)-N-methylamino]-3-(biphenyl-4-yl)propionyl)-4-benzylpiperidine-4-carboxylic acid ethyl ester



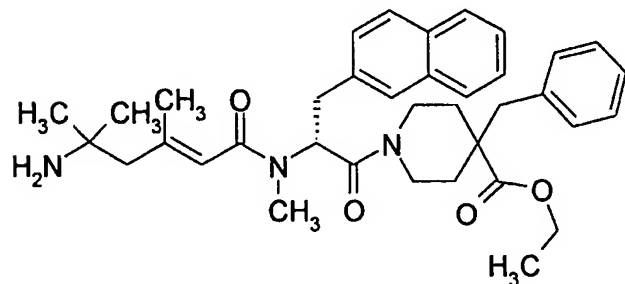
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1-((2R)-2-[N-((2E)-5-Amino-5-methylhex-2-enoyl)-N-methylamino]-3-(2-naphthyl)propionyl)-4-benzylpiperidine-4-carboxylic acid ethyl ester



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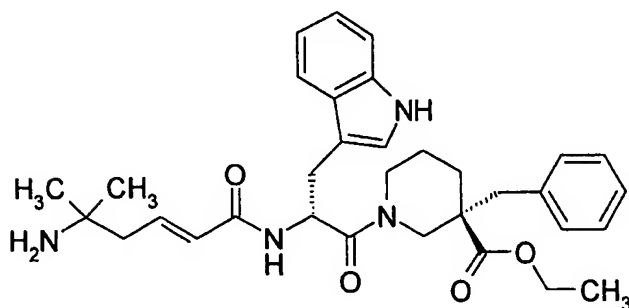
1-((2R)-2-[N-((2E)-5-Amino-3,5-dimethylhex-2-enoyl)-N-methylamino]-3-(2-naphthyl)propionyl)-4-benzylpiperidine-4-carboxylic acid ethyl ester



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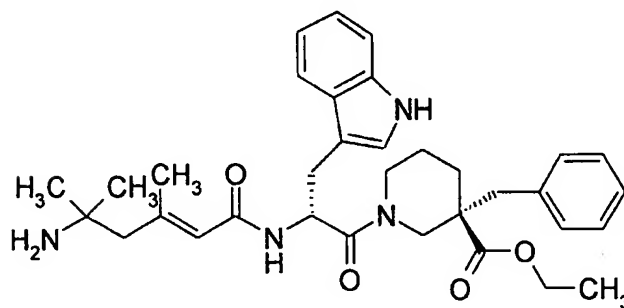
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(3S)-1-[(2R)-2-((2E)-5-Amino-5-methylhex-2-enoylamino)-3-(1H-indol-3-yl)propionyl]-3-benzylpiperidine-3-carboxylic acid ethyl ester



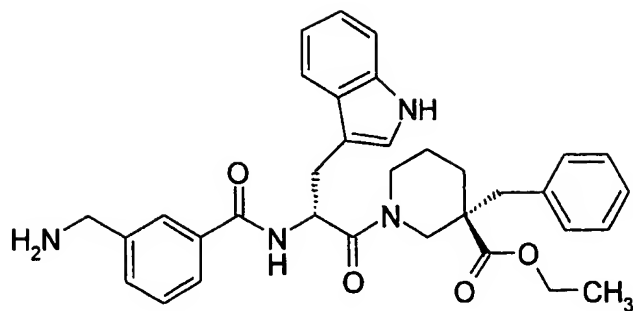
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(3S)-1-[(2R)-2-((2E)-5-Amino-3,5-dimethylhex-2-enoylamino)-3-(1H-indol-3-yl)propionyl]-3-benzylpiperidine-3-carboxylic acid ethyl ester



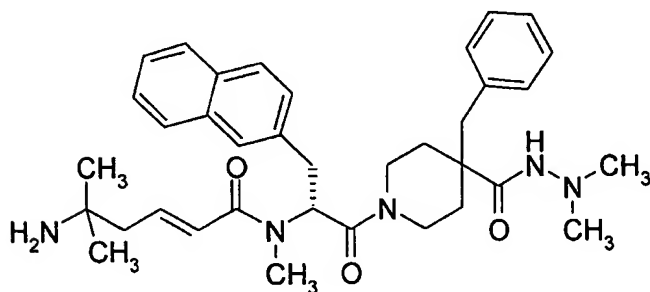
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(3S)-1-[(2R)-2-(3-(Aminomethyl)benzoylamino)-3-(1H-indol-3-yl)propionyl]-3-benzylpiperidine-3-carboxylic acid ethyl ester

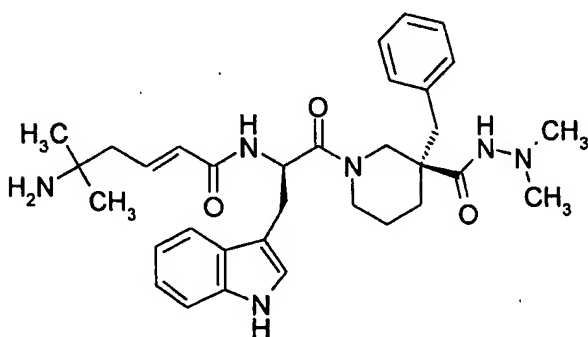


(2E)-5-Amino-5-methylhex-2-enoic acid N-((1R)-2-[4-benzyl-4-(N',N'-dimethylhydrazinocarbonyl)piperidin-1-yl]-1-((2-naphthyl)methyl)-2-oxoethyl)-N-methylamide

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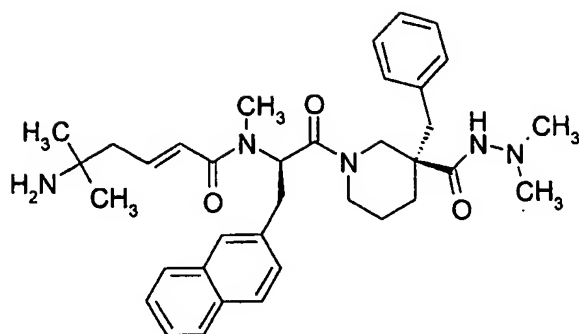


(2E)-5-Amino-5-methylhex-2-enoic acid N-((1R)-2-[3-benzyl-3-(N',N'-dimethylhydrazinocarbonyl)-piperidin-1-yl]-1-((1H-indol-3-yl)methyl)-2-oxoethyl)amide



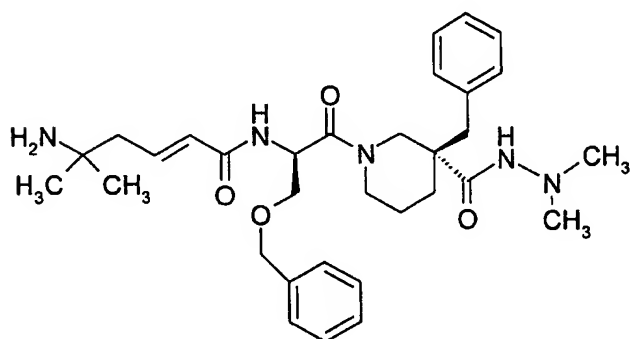
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(2E)-5-Amino-5-methylhex-2-enoic acid N-((1R)-2-[3-benzyl-3-(N',N'-dimethylhydrazinocarbonyl)-piperidin-1-yl]-1-((2-naphthyl)methyl)-2-oxoethyl)-N-methylamide



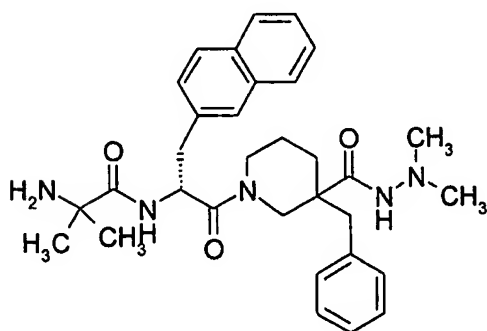
(2E)-5-Amino-5-methylhex-2-enoic acid {(1R)-2-[3-benzyl-3-(N',N'-dimethylhydrazinocarbonyl)piperidin-1-yl]-1-(benzyloxymethyl)-2-oxoethyl}amide

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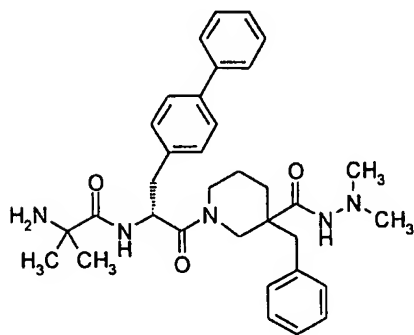
2-Amino-N-{2-[3-benzyl-3-(N',N'-dimethylhydrazinocarbonyl)piperidin-1-yl]-1-((2-naphthyl)methyl)-2-oxo-ethyl}-2-methyl-propionamide

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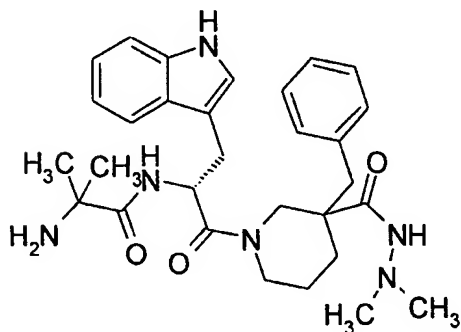
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2-Amino-N-((1R)-2-[3-benzyl-3-(N',N'-dimethylhydrazinocarbonyl)piperidin-1-yl]-1-((biphenyl-4-yl)methyl)-2-oxoethyl)-2-methylpropionamide



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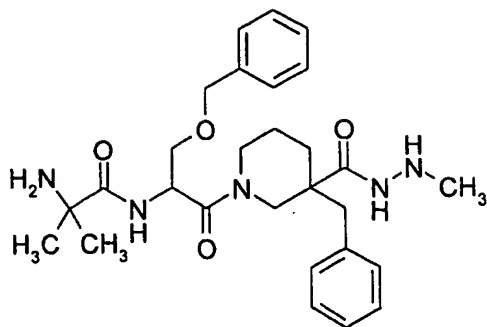
2-Amino-N-((1R)-2-[3-benzyl-3-(N',N'-dimethylhydrazinocarbonyl)piperidin-1-yl]-1-((1H-indol-3-yl)methyl)-2-oxoethyl)-2-methylpropionamide



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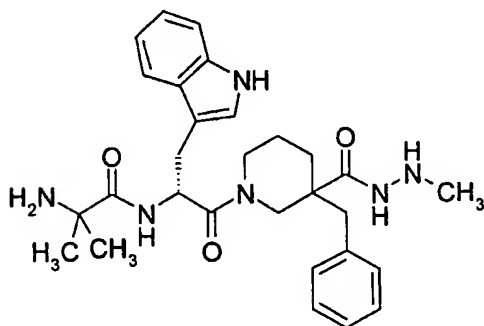
2-Amino-N-2-[3-benzyl-3-(N'-dimethylhydrazinocarbonyl)piperidin-1-yl]-1-(benzyloxymethyl)-2-oxoethyl)-2-methylpropionamide





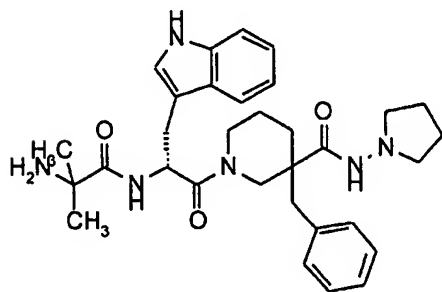
2-Amino-N-((1R)-2-[3-benzyl-3-(N',N'-dimethylhydrazinocarbonyl)piperidin-1-yl]-1-(benzyloxymethyl)-2-oxoethyl)-2-methylpropionamide

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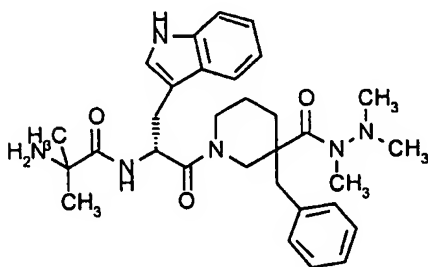


1-[(2R)-2-(2-Amino-2-methylpropionylamino)-3-(1-H-indol-3-yl)propionyl]-3-benzylpiperidine-3-carboxylic acid (pyrrolidin-1-yl)amide

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2-Amino-N-((1R)-2-[3-benzyl-3-(N,N',N'-trimethylhydrazinocarbonyl)piperidin-1-yl]-1-(benzyloxymethyl)-2-oxoethyl)-2-methylpropionamide

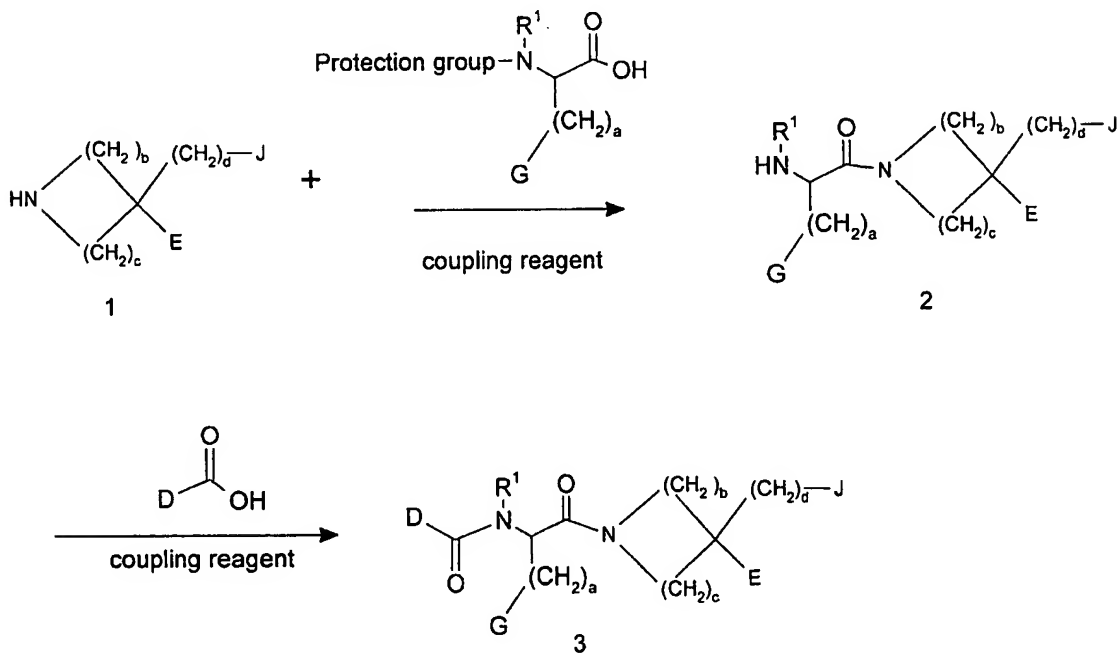


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and pharmaceutically acceptable salts thereof.

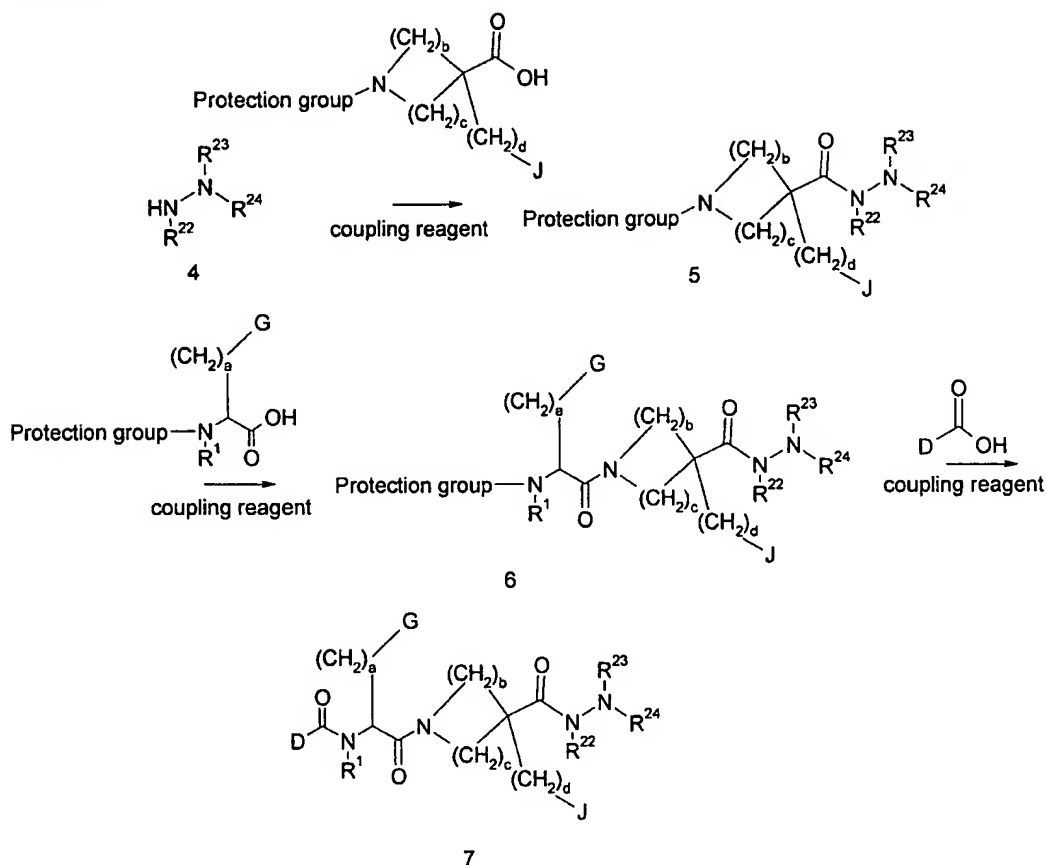
### General Method

10 Scheme I



The procedures used in this patent and illustrated in above scheme I are based on peptide couplings well known in the art, and should in no way be interpreted as limiting the invention in any way. In the first step an amine (1) and a carboxylic acid is coupled to an amide by a coupling agent such as a carbodiimide and hydroxyazabenzotriazole (HOAt). Prior to the  
5 next coupling a suitable protecting group such as tert butyloxycarbonyl (Boc) can be removed with methods well known to those skilled in the art, thereby producing compound (2). It is also possible to avoid the use of protecting groups. Hereafter (2) is coupled to a carboxylic acid of formula D-COOH by a coupling agent, thereby producing compound (3).

Scheme II



Compounds of the general structure I containing a hydrazine in the C-terminal may be prepared as illustrated above in scheme II. The procedures used in this patent and illustrated in

above scheme II are based on peptide couplings well known in the art, and should in no way be interpreted as limiting the invention in any way. In the first step a mono-, di- or tri-

substituted hydrazine or hydrazone (4) and an appropriate protected amino acid are coupled to form a compound (5) using a suitable coupling reagent such as 1-ethyl-3-(3-

dimethylaminopropyl)carbodiimide hydrochloride, 1-hydroxybenzotriazole or another coupling reagent known in the art of peptide coupling in an appropriate solvent such as di-

methylformamid or dichloromethane. Hereafter, the amide (5) and a carboxylic acid is coupled by a coupling agent, thereby producing compound (6). Hereafter (6) is coupled to a car-

boxylic acid of formula D-COOH by a coupling agent, thereby producing compound (7). In the procedure, prior to the next coupling a suitable protecting group such as tert butyloxy-

carbonyl (Boc) can be removed with methods well known to those skilled in the art. It is also possible to avoid the use of protecting groups. The appropriate amino acids may be pro-

tected and deprotected by methods known in the art and described by e.g. T.W. Green (Protective Groups in Organic Synthesis, 2. Ed., John Wiley and Sons, New York 1991).

The compounds of formula I exhibit an improved resistance to proteolytic degradation by enzymes because they are non-natural, in particular because the natural amide bonds are replaced by non-natural amide bond mimetics. The increased resistance to proteolytic degradation of the compounds of the invention in comparison with known hormone releasing peptides is expected to improve their bioavailability compared to that of the peptides suggested in the prior literature.

In the above structural formulas and throughout the present specification, the following terms have the indicated meanings:

The C<sub>1-6</sub>-alkyl, C<sub>1-6</sub>-alkylene, C<sub>1-4</sub>-alkyl or C<sub>1-4</sub>-alkylene groups specified above are intended to include those alkyl or alkylene groups of the designated length in either a linear or branched or cyclic configuration. Examples of linear alkyl are methyl, ethyl, propyl, butyl, pentyl, and hexyl and their corresponding divalent moieties, such as ethylene. Examples of branched alkyl are isopropyl, sec-butyl, tert-butyl, isopentyl, and isohexyl and their corresponding divalent moieties, such as isopropylene. Examples of cyclic alkyl are C<sub>3-6</sub>-cycloalkyl such as cyclopropyl, cyclobutyl, cyclopentyl and cyclohexyl and their corresponding divalent moieties, such as cyclopropylene.

The C<sub>1-6</sub>-alkoxy groups specified above are intended to include those alkoxy groups of the designated length in either a linear or branched or cyclic configuration. Examples of linear alkoxy are methoxy, ethoxy, propoxy, butoxy, pentoxy, and hexoxy. Examples of branched alkoxy are isopropoxy, sec-butoxy, tert-butoxy, isopentoxy, and isohexoxy. Examples of cyclic alkoxy are cyclopropyloxy, cyclobutyloxy, cyclopentyloxy and cyclohexyloxy.

The C<sub>1-7</sub>-acyl groups specified above are intended to include those acyl groups of the designated length in either a linear or branched or cyclic configuration. Examples of linear acyl are formyl, acetyl, propionyl, butyryl, valeryl, etc. Examples of branched are isobutyryl, isovaleryl, pivaloyl, etc. Examples of cyclic are cyclopentylcarbonyl, cyclohexylcarbonyl, etc.

In the present context, the term "aryl" is intended to include monovalent carbocyclic aromatic ring moieties, being either monocyclic, bicyclic or polycyclic, e.g. selected from the group consisting of phenyl and naphthyl, optionally substituted with one or more C<sub>1-6</sub>-alkyl, C<sub>1-6</sub>-alkoxy, halogen, amino or aryl.

5

In the present context, the term "arylene" is intended to include divalent carbocyclic aromatic ring moieties, being either monocyclic, bicyclic or polycyclic, e.g. selected from the group consisting of phenylene and naphthylene, optionally substituted with one or more C<sub>1-6</sub>-alkyl, C<sub>1-6</sub>-alkoxy, halogen, amino or aryl.

10

In the present context, the term "hetaryl" is intended to include monovalent heterocyclic aromatic ring moieties, being either monocyclic, bicyclic or polycyclic, e.g. selected from the group consisting of pyridyl, 1-H-tetrazol-5-yl, thiazolyl, imidazolyl, indolyl, pyrimidinyl, thiadiazolyl, pyrazolyl, oxazolyl, isoxazolyl, oxadiazolyl, thienyl, quinolinyl, pyrazinyl, or isothiazolyl, optionally substituted by one or more C<sub>1-6</sub>-alkyl, C<sub>1-6</sub>-alkoxy, halogen, amino or aryl.

15

In the present context, the term "hetarylene" is intended to include divalent heterocyclic aromatic ring moieties, being either monocyclic, bicyclic or polycyclic, e.g. selected from the group consisting of pyridinediyl, 1-H-tetrazolediyl, thiazoldiyl, imidazolediyl, indolediyl, pyrimidinediyl, thiadiazolelediyl, pyrazolelediyl, oxazolelediyl, isoxazolelediyl, oxadiazolelediyl, thiophenediyl, quinolinediyl, pyrazinediyl, or isothiazolelediyl, optionally substituted by one or more C<sub>1-6</sub>-alkyl, C<sub>1-6</sub>-alkoxy, halogen, amino or aryl.

20

In the present context, the term "heterocyclic system" is intended to include aromatic as well as non-aromatic ring moieties, which may be monocyclic, bicyclic or polycyclic, and contain in their ring structure at least one, such as one, two or three, nitrogen atom(s), and optionally one or more, such as one or two, other hetero atoms, e.g. sulphur or oxygen atoms. The heterocyclic system is preferably selected from pyrazole, pyridazine, triazine, indazole, phthalazine, cinnoline, pyrazolidine, pyrazoline, aziridine, dithiazine, pyrrol, imidazol, pyrazole, isoindole, indole, indazole, purine, pyrrolidine, pyrroline, imidazolidine, imidazoline, pyrazolidine, pyrazoline, piperidine, piperazine, indoline, isoindoline, or morpholine.

25

30

The term "halogen" is intended to include chlorine (Cl), fluorine (F), bromine (Br) and iodine (I).

The compounds of the present invention may have one or more asymmetric centres (chiral carbon atoms) and it is intended that stereoisomers, as separated, pure or partially purified stereoisomers or racemic mixtures thereof are included in the scope of the invention.

5

The compounds of the present invention may optionally be on a pharmaceutically acceptable salt form such as the pharmaceutically acceptable acid addition salts of compounds of formula I which include those prepared by reacting the compound of formula I with an inorganic or organic acid such as hydrochloric, hydrobromic, sulfuric, acetic, phosphoric, lactic, maleic, mandelic phthalic, citric, glutaric, gluconic, methanesulfonic, salicylic, succinic, tartaric, toluenesulfonic, trifluoroacetic, sulfamic or fumaric acid and/or water.

The compounds of formula I may be administered in pharmaceutically acceptable acid addition salt form or, where appropriate, as a alkali metal or alkaline earth metal or lower alkylammonium salt. Such salt forms are believed to exhibit approximately the same order of activity as the free base forms.

In another aspect, the present invention relates to a pharmaceutical composition comprising, as an active ingredient, a compound of the general formula I or a pharmaceutically acceptable salt thereof together with a pharmaceutically acceptable carrier or diluent.

Pharmaceutical compositions containing a compound of the present invention may be prepared by conventional techniques, e.g. as described in Remington's Pharmaceutical Sciences, 1985 or in Remington: The Science and Practice of Pharmacy, 19th Edition (1995). The compositions may appear in conventional forms, for example capsules, tablets, aerosols, solutions, suspensions or topical applications.

The pharmaceutical carrier or diluent employed may be a conventional solid or liquid carrier. Examples of solid carriers are lactose, terra alba, sucrose, cyclodextrin, talc, gelatin, agar, pectin, acacia, magnesium stearate, stearic acid or lower alkyl ethers of cellulose. Examples of liquid carriers are syrup, peanut oil, olive oil, phospholipids, fatty acids, fatty acid amines, polyoxyethylene or water.

Similarly, the carrier or diluent may include any sustained release material known in the art, such as glyceryl monostearate or glyceryl distearate, alone or mixed with a wax.

If a solid carrier is used for oral administration, the preparation may be tableted, placed in a hard gelatin capsule in powder or pellet form or it can be in the form of a troche or lozenge. The amount of solid carrier will vary widely but will usually be from about 25 mg to about 1 g. If a liquid carrier is used, the preparation may be in the form of a syrup, emulsion, soft gelatin capsule or sterile injectable liquid such as an aqueous or non-aqueous liquid suspension or solution.

10

A typical tablet which may be prepared by conventional tableting techniques may contain:

Core:

	Active compound (as free compound or salt thereof)	100mg
15	Colloidal silicon dioxide (Aerosil)	1.5mg
	Cellulose, microcryst. (Avicel)	70mg
	Modified cellulose gum (Ac-Di-Sol)	7.5mg
	Magnesium stearate	

20 

Coating:

	HPMC approx.	9mg
	*Mywacett 9-40 T approx.	0.9mg

\*Acylated monoglyceride used as plasticizer for film coating.

25

For nasal administration, the preparation may contain a compound of formula I dissolved or suspended in a liquid carrier, in particular an aqueous carrier, for aerosol application. The carrier may contain additives such as solubilizing agents, e.g. propylene glycol, surfactants, absorption enhancers such as lecithin (phosphatidylcholine) or cyclodextrin, or preservatives such as parabenes.

30



Generally, the compounds of the present invention are dispensed in unit dosage form comprising 50-200 mg of active ingredient together with a pharmaceutically acceptable carrier per unit dosage.

- 5 The dosage of the compounds according to this invention is suitably 0.01-500 mg/day, e.g. from about 5 to about 50 mg, such as about 10 mg per dose, when administered to patients, e.g. humans, as a drug.

In a further aspect the present invention relates to a pharmaceutical composition in unit dose  
10 form, comprising as an active ingredient from about 10 to about 200 mg of the compound of the general formula I or a pharmaceutically acceptable salt thereof.

It has been demonstrated that compounds of the general formula I possess the ability to release endogenous growth hormone *in vivo*. The compounds may therefore be used in the  
15 treatment of conditions which require increased plasma growth hormone levels such as in growth hormone deficient humans or in elderly patients or livestock.

Thus, in a particular aspect, the present invention relates to a pharmaceutical composition for stimulating the release of growth hormone from the pituitary, the composition comprising, as an  
20 active ingredient, a compound of the general formula I or a pharmaceutically acceptable salt thereof together with a pharmaceutically acceptable carrier or diluent.

In a further aspect, the present invention relates to a method of stimulating the release of growth hormone from the pituitary, the method comprising administering to a subject in need  
25 thereof an effective amount of a compound of the general formula I or a pharmaceutically acceptable salt thereof.

In a still further aspect, the present invention relates to the use of a compound of the general formula I or a pharmaceutically acceptable salt thereof for the preparation of a medicament for  
30 stimulating the release of growth hormone from the pituitary.

To those skilled in the art, it is well known that the current and potential uses of growth hormone in humans are varied and multitudinous. Thus, compounds of formula I can be adminis-

tered for purposes stimulating release of growth hormone from the pituitary and would then have similar effects or uses as growth hormone itself. Compounds of formula I are useful for stimulation of growth hormone release in the elderly; prevention of catabolic side effects of glucocorticoids, prevention and/or treatment of osteoporosis, treatment of chronic fatigue syndrome (CFS), treatment of acute fatigue syndrome and muscle loss following election surgery, stimulation of the immune system, acceleration of wound healing, accelerating bone fracture repair, accelerating complicated fractures, e.g. distraction osteogenesis, treatment of wasting secondary to fractures, treatment of growth retardation, treating of growth retardation resulting from renal failure or insufficiency, treatment of cardiomyopathy, treatment of chronic liver disease, treatment of thrombocytopenia, treatment of Crohn's disease, treatment of short bowel syndrome, treatment of chronic obstructive pulmonary disease (COPD), treatment of complications associated with transplantation, treatment of physiological short stature including growth hormone deficient children and short stature associated with chronic illness, treatment of obesity and growth retardation associated with obesity, treatment of anorexia, treating growth retardation associated with the Prader-Willi syndrome and Turner's syndrome; increasing the growth rate of a patient having partial growth hormone insensitive syndrome, accelerating the recovery and reducing hospitalization of burn patients; treatment of intrauterine growth retardation, skeletal dysplasia, hypercortisolism and Cushing's syndrome; induction of pulsatile growth hormone release; replacement of growth hormone in stressed patients, treatment of osteochondrodysplasias, Noonan's syndrome, schizophrenia, depressions, Alzheimer's disease, delayed wound healing and psychosocial deprivation, treatment of pulmonary dysfunction and ventilator dependency, treatment of cardiac failure or related vascular dysfunction, treatment of impaired cardiac function, treatment or prevention of myocardial infarction, lowering blood pressure, protection against ventricular dysfunction or prevention of reperfusion events, treatment of adults in chronic dialysis, attenuation of protein catabolic responses after major surgery, reducing cachexia and protein loss due to chronic illness such as cancer or AIDS; treatment of hyperinsulinemia including nesidioblastosis, adjuvant treatment for ovulation induction; to stimulate thymic development and prevent the age-related decline of thymic function, treatment of immunosuppressed patients, treatment of sarcopenia, treatment of wasting in connection with AIDS, improvement in muscle strength, mobility, maintenance of skin thickness, metabolic homeostasis, renal homeostasis in the frail elderly, stimulation of osteoblasts, bone remodelling and cartilage growth, regulation of food intake, stimulation of the immune system in companion animals and treatment of disorder of aging in companion animals, promoting

growth in livestock and stimulation of wool growth in sheep, treatment of metabolic syndrom (syndrom X), treatment of insulin resistance, including NIDDM, in mammals, e.g. humans, improvement of sleep quality and correction of the relative hyposomatotropism of senescence due to high increase in REM sleep and a decrease in REM latency, and treatment of hypothermia. Treatment is also intended to include prophylactic treatment.

For the above indications the dosage will vary depending on the compound of formula I employed, on the mode of administration and on the therapy desired. However, generally dosage levels between 0.0001 and 100 mg/kg body weight daily are administered to patients and animals to obtain effective release of endogenous growth hormone. Moreover the compounds of formula I have no or substantially no side-effects, when administered in the above dosage levels, such side-effects being e.g. release of LH, FSH, TSH, ACTH, vasopressin, oxytocin, cortisol and/or prolactin. Usually, dosage forms suitable for oral, nasal, pulmonal or transdermal administration comprise from about 0.0001 mg to about 100 mg, preferably from about 0.001 mg to about 50 mg of the compounds of formula I admixed with a pharmaceutically acceptable carrier or diluent.

Optionally, the pharmaceutical composition of the invention may comprise a compound of formula I combined with one or more compounds exhibiting a different activity, e.g., an antibiotic or other pharmacologically active material.

The route of administration may be any route which effectively transports the active compound to the appropriate or desired site of action, such as oral, nasal, pulmonary, transdermal or parenteral, the oral route being preferred.

Apart from the pharmaceutical use of the compounds of formula I, they may be useful in vitro tools for investigating the regulation of growth hormone release.

Compounds of formula I may also be useful in vivo tools for evaluating the growth hormone releasing capability of the pituitary. For example, serum samples taken before and after administration of these compounds to humans can be assayed for growth hormone. Comparison of the growth hormone in each serum sample would directly determine the ability of the patients pituitary to release growth hormone.

Compounds of formula I may be administered to commercially important animals to increase their rate and extent of growth, and to increase milk production.

- 5 A further use of growth hormone secretagogue compounds of formula I is in combination with other secretagogues such as GHRP (2 or 6), GHRH and its analogues, growth hormone and its analogues or somatomedins including IGF-1 and IGF-2.

## Pharmacological Methods

Compounds of formula I may be evaluated in vitro for their efficacy and potency to release growth hormone in rat pituitary primary cultures, and such evaluation may be performed as described below.

The isolation of rat pituitary cells is a modification of O. Sartor et al., Endocrinology **116**, 1985, pp. 952-957. Male albino Sprague-Dawley rats (250 +/- 25 grams) were purchased from Møllegaard, Lille Skensved, Denmark. The rats were housed in group cages (four animals/cage) and placed in rooms with 12 hour light cycle. The room temperature varied from 19-24°C and the humidity from 30 - 60%.

The rats were decapitated and the pituitaries dissected. The neurointermediate lobes were removed and the remaining tissue was immediately placed in icecold isolation buffer (Gey's medium (Gibco 041-04030) supplemented with 0.25% D-glucose, 2% non-essential amino acids (Gibco 043-01140) and 1% bovine serum albumine (BSA) (Sigma A-4503)). The tissue was cut into small pieces and transferred to isolation buffer supplemented with 3.8 mg/ml of trypsin (Worthington #3707 TRL-3) and 330 mg/ml of DNase (Sigma D-4527). This mixture was incubated at 70 rotations/min for 35 min at 37°C in a 95/5% atmosphere of O<sub>2</sub>/CO<sub>2</sub>. The tissue was then washed three times in the above buffer. Using a standard pasteur pipette, the tissue was then aspirated into single cells. After dispersion, cells were filtered through a nylon filter (160 mm) to remove undigested tissue. The cell suspension was washed 3 times with isolation buffer supplemented with trypsin inhibitor (0.75 mg/ml, Worthington #2829) and finally resuspended in culture medium; DMEM (Gibco 041-01965) supplemented with 25 mM HEPES (Sigma H-3375), 4 mM glutamine (Gibco 043-05030H), 0.075% sodium bicarbonate (Sigma S-8875), 0.1% non-essential amino acid, 2.5% fetal calf serum (FCS, Gibco 011-06290), 3% horse serum (Gibco 034-06050), 10% fresh rat serum, 1 nM T<sub>3</sub> (Sigma T-2752) and 40 mg/l dexamethasone (Sigma D-4902) pH 7.3, to a density of 2 x 10<sup>5</sup> cells/ml. The cells were seeded into microtiter plates (Nunc, Denmark), 200 ml/well, and cultured for 3 days at 37°C and 8% CO<sub>2</sub>.

### Compound testing

After culturing, the cells were washed twice with stimulation buffer (Hanks Balanced Salt Solution (Gibco 041-04020) supplemented with 1% BSA (Sigma A-4503), 0.25% D-glucose (Sigma G-5250) and 25 mM HEPES (Sigma H-3375) pH 7.3) and preincubated for 1 hour at 37°C. The  
5 buffer was exchanged with 90 ml stimulation buffer (37°C). Ten ml test compound solution was added and the plates were incubated for 15 min at 37°C and 5% CO<sub>2</sub>. The medium was decanted and analyzed for GH content in an rGH SPA test system.

10 All compounds were tested in doses ranging from 10 pM to 100 mM. A dose-response relation was constructed using the Hill equation (Fig P, Biosoft). The efficacy (maximal GH released, E<sub>max</sub>) was expressed in % of the E<sub>max</sub> of GHRP-6. The potency (EC<sub>50</sub>) was determined as the concentration inducing half maximal stimulation of the GH release.

15 Compounds of formula I may be evaluated for their metabolic stability using the procedure described below:

Compounds is dissolved at a concentration of 1 mg/ml in water. 25 ml of this solution is added to 175 ml of the respective enzyme-solution (resulting in an enzyme:substrate ratio (w/w) of  
20 approximately 1:5). The solution is left at 37°C overnight. 10 ml of the various degradation solutions is analyzed against a corresponding zero-sample using flow injection electrospray mass spectrometry (ESMS) with selected ion monitoring of the molecular ion. If the signal has decreased more than 20% compared to the zero-sample, the remainder of the solution is analyzed by HPLC and mass spectrometry in order to identify the extent and site(s) of degradation  
25 precisely.

Several standard peptides (ACTH 4-10, Angiotensin 1-14 and Glucagon) have been included in the stability tests in order to verify the ability of the various solutions to degrade peptides.

30 Standard peptides (angiotensin 1-14, ACTH 4-10 and glucagon) were purchased from Sigma, MO, USA)

Enzymes (trypsin, chymotrypsin, elastase aminopeptidase M and carboxypeptidase Y and B) were all purchased from Boehringer Mannheim GmbH (Mannheim, Germany)

5 Pancreatic enzyme mix: trypsin, chymotrypsin and elastase in 100 mM ammoniumbicarbonate pH 8.0 (all concentrations 0.025 mg/ml).

Carboxypeptidase mix: carboxypeptidase Y and B in 50 mM ammoniumacetate pH 4.5 (all concentrations 0.025 mg/ml).

10 Aminopeptidase M solution: aminopeptidase M (0.025 mg/ml) in 100 mM ammoniumbicarbonate pH 8.0

Mass spectrometric analysis was performed using two different mass spectrometers. A Sciex API III triple quadrupole LC-MS instrument (Sciex instruments, Thornhill, Ontario) equipped  
15 with an electrospray ion-source and a Bio-Ion 20 time-of-flight Plasma Desorption instrument (Bio-Ion Nordic AB, Uppsala, Sweden).

Quantification of the compounds (before and after degradation) was done on the API III instrument using single ion monitoring of the molecular ion in question with flow injection of the  
20 analyte. The liquid flow (MeOH:water 1:1) of 100 ml/min was controlled by an ABI 140B HPLC unit (Perkin-Elmer Applied Biosystems Divisions, Foster City, CA). The instrument parameters were set to standard operation conditions, and SIM monitoring was performed using the most intense molecular ion (in most cases this corresponded to the doubly charged molecular ion).

25 Identification of degradation products furthermore involved the use of plasma desorption mass spectrometry (PDMS) with sample application on nitrocellulose coated targets and standard instrumental settings. The accuracy of the hereby determined masses is generally better than 0.1%.

30 Separation and isolation of degradation products was done using a HY-TACH C-18 reverse phase 4.6x105 mm HPLC column (Hewlett-Packard Company, Palo Alto, CA) with a standard acetonitril: TFA separation gradient. The HPLC system used was HP1090M (Hewlett-Packard Company, Palo Alto, CA).

Peptide derivative	MW/SIM ion (amu)	Carboxy - peptidase mix	Pan. Enzyme mix
Standards			
ACTH 4-10	1124.5/562.8	+	-
Glucagon	3483/871.8	-	-
Insulin (B23-29)	859.1/430.6		
Angiotensin 1-14	1760.1/881.0	-	-
GHRP-2	817.4/409.6	-	-
GHRP-6	872.6/437.4	-	-

+: Stable (less than 20% decrease in SIM signal after 24 h in degradation solution)

-: Unstable (more than 20% decrease in SIM signal after 24 h in degradation solution)

5

Any novel feature or combination of features described herein is considered essential to this invention.

#### EXAMPLES:

10

The process for preparing compounds of formula I and preparations containing them is further illustrated in the following examples, which however, are not to be construed as limiting.



The structures of the compounds are confirmed by either High Performance Liquid Chromatography (HPLC), nuclear magnetic resonance (NMR, Bruker 400 MHz) or Liquid Chromatography-Mass Spectrometry (LC-MS). NMR shifts ( $\delta$ ) are given in parts per million (ppm) and only selected peaks are given. mp is melting point and is given in  $^{\circ}\text{C}$ . Column chromatography was carried out using the technique described by W.C. Still et al, J. Org. Chem. 1978, 43, 2923-2925 on Merck silica gel 60 (Art 9385). Compounds used as starting materials are either known compounds or compounds which can readily be prepared by methods known per se. The methanol/ammonia solution used is a 10% ammonia solution in methanol.

#### HPLC-Analysis:

##### Method A1.

The RP-analysis was performed using UV detections at 214, 254, 276, and 301 nm on a 218TP54 4.6 mm x 250 mm 5m C-18 silica column (The Separations Group, Hesperia), which was eluted at 1 mL/min at  $42^{\circ}\text{C}$ . The column was equilibrated with 5% acetonitrile in a buffer consisting of 0.1 M ammonium sulfate, which was adjusted to pH 2.5 with 4M sulfuric acid. after injection the sample was eluted by a gradient of 5% to 60% acetonitrile in the same buffer during 50 min.

##### Method B1.

The RP-analysis was performed using UV detections at 214, 254, 276, and 301 nm on a 218TP54 4.6 mm x 250 mm 5m C-18 silica column (The Separations Group, Hesperia), which was eluted at 1 mL/min at  $42^{\circ}\text{C}$ . The column was equilibrated with 5% (acetonitrile + 0.1 % TFA) in an aqueous solution of TFA in water (0.1%). After injection the sample was eluted by a gradient of 5% to 60% (acetonitrile + 0.1% TFA) in the same aqueous buffer during 50 min.

#### LC-MS-Analysis:

The LC-MS analyses were performed on a PE Sciex API 100 LC/MS System using a Waters® 3 mm x 150 mm 3.5 m C-18 Symmetry column and positive ionspray with a flow rate

of 20 ml/min. The column was eluted with a linear gradient of 5-90% acetonitrile, 85-0% water and 10 % trifluoroacetic acid (0.1%)/ water in 15 min at a flow rate of 1 ml/min.

5 Abbreviations:

TLC: thin layer chromatography

DMSO: dimethylsulfoxide

min: minutes

h: hours

10 Boc: tert butyloxycarbonyl

DMF: dimethylformamide

THF: tetrahydrofuran

EDAC: N-ethyl-N'-dimethylaminopropylcarbodiimide hydrochloride

HOAt: 1-hydroxy-7-azabenzotriazole

15 DIEA: diisopropylethylamine

TFA: trifluoroacetic acid

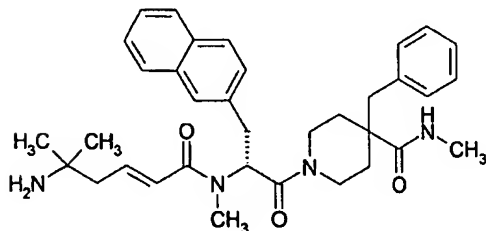
Buildingblocks:

N-methylated aminoacids used in the following examples were prepared as in Can. J. Chem.

20 1977, 55, 906.

Example 1

1-((2R)-2-[N-((2E)-5-Amino-5-methylhex-2-enoyl)-N-methylamino]-3-(2-naphthyl)propionyl)-  
25 4-benzylpiperidine-4-carboxylic acid methylamide



## Step A

*N*-*tert*-butyloxycarbonyl-4-benzylpiperidine-4-carboxylic acid

- 5 *N*-*tert*-butyloxycarbonyl-4-benzylpiperidine-4-carboxylic acid ethyl ester (prepared as in Gilligan et al J. Med. Chem. 1994, 364-370 using benzyl bromide as the alkylating agent) (11.0 g; 32 mmol) was refluxed for 7 h. in a mixture of ethanol (190 ml) and aqueous sodium hydroxide (18% 190 ml). The volume was reduced to a third in vacuo and pH was adjusted to 3 with sodium hydrogen sulphate. Water (300 ml) was added and the mixture was extracted  
10 with ethylacetate (2 x 250 ml). The combined organic phases were evaporated to afford 8.6 g of *N*-*tert*-butyloxycarbonyl-4-benzylpiperidine-4-carboxylic acid.

<sup>1</sup>H-NMR: d (CDCl<sub>3</sub>) 1.45 (s, 9H); 1.5 (m(br); 2H); 2.08 (m(br); 2H); 2.88 (m(br); 2H); 2.89 (s, 2H); 3.95 (m(br); 2H); 7.09-7.30 (5 arom. H).

15

## Step B

4-Benzyl-4-methylcarbamoylpiperidine-1-carboxylic acid *tert*-butyl ester

- 20 *N*-*tert*-butyloxycarbonyl-4-benzylpiperidine-4-carboxylic acid (3.0 g; 9.0 mmol) was dissolved in methylene chloride (25 ml) and EDAC (1.8 g; 9.0 mmol) and HOAt (1.3 g; 9.0 mmol) was added. The mixture was stirred for 15 min, then methyl amine (33% in ethanol; 2.3 ml; 18 mmol) and DIEA (1.6 ml; 9.0 mmol) was added and the mixture was stirred overnight. Methylene chloride (100 ml) was added and the mixture was washed with a saturated aqueous  
25 solution of sodium hydrogen carbonate (50 ml) and a aqueous solution of sodium hydrogen-sulphate (10%, 50 ml), dried (MgSO<sub>4</sub>) and evaporated in vacuo. The residue was chromatographed on silica (90 g) using a mixture of aqueous ammonia/ethanol/methylene chloride (1:7:92) as eluent to afford 2.8 g of 4-benzyl-4-methylcarbamoylpiperidine-1-carboxylic acid *tert*-butyl ester.

30

<sup>1</sup>H-NMR: d (CDCl<sub>3</sub>) 1.44 (s, 9H); 1.55 (m(br); 2H); 1.98 (m(br); 2H); 2.70 (d, 3H); 2.98 (m(br); 2H); 2.89 (s, 2H); 3.87 (m(br); 2H); 5.15 (q(br); 1H); 7.01-7.32 (5 arom. H).

## Step C

## 4-Benzylpiperidine-4-carboxylic acid methylamide

- 5 4-Benzyl-4-methylcarbamoylpiperidine-1-carboxylic acid tert-butyl ester (2.8 g) was dissolved in a mixture of TFA and methylene chloride and stirred for 40 min. The solvent was removed in vacuo and the residue was dissolved in water (30 ml) and pH was adjusted to 13 with aqueous sodium hydroxide (1N). The aqueous phase was extracted with methylene chloride (3 x 75 ml) and the combined organic phases were dried (MgSO<sub>4</sub>) and evaporated  
10 in vacuo to afford 1.50 g of 4-benzylpiperidine-4-carboxylic acid methylamide.

<sup>1</sup>H-NMR: d (CDCl<sub>3</sub>) 1.80 (td; 2H); 2.14 (d(br), 2H); 2.70 (d, 3H); 2.81 (s, 2H); 2.85 (dt; 2H); 3.21 (dt, 2H); 5.25 (t, 1H); 7.00-7.35 (5 arom. H).

## Step D

15

## 4-Benzyl-1-((2R)-2-methylamino-3-(2-naphthyl)propionyl)piperidine-4-carboxylic acid methylamide

- (2R)-2-*tert*-Butyloxycarbonylamino-N-methyl-3-(2-naphthyl)propionic acid (709 mg; 2.15  
20 mmol), HOAt (293 mg 2.25 mmol) and EDAC (412 mg; 2.25 mmol) were dissolved in methylene chloride (5ml) and stirred for 15 min. 4-Benzylpiperidine-4-carboxylic acid methylamide (500 mg; 2.25 mmol) and DIEA (0.35 ml) were added and the mixture was stirred overnight. Methylene chloride (30 ml) was added and the mixture was washed with a saturated aqueous solution of sodium hydrogen carbonate (20 ml) and a aqueous solution of sodium hydrogensulphate (10%, 20 ml), dried (MgSO<sub>4</sub>) and evaporated in vacuo. The residue was chromatographed on silica (40 g) using ethyl acetate as eluent to afford 810 mg of 4-benzyl-1-  
25 ((2R)-2-(N-methyl-*tert*-butyloxycarbonylamino)-3-(2-naphthyl)propionyl)piperidine-4-carboxylic acid methylamide which was dissolved in TFA/methylene chloride (8+8 ml) and stirred for 40 min at RT. The solvent was removed in vacuo and the residue was neutralised  
30 with a saturated solution of sodium hydrogen carbonate and extracted with ethyl acetate (50 ml). The organic phase was dried (MgSO<sub>4</sub>) and evaporated to afford 729 mg of 4-benzyl-1-((2R)-2-methylamino-3-(2-naphthyl)propionyl)piperidine-4-carboxylic acid methylamide.

## Step E

4-Benzyl-1-((2R)-2-methylamino-3-(2-naphthyl)propionyl)piperidine-4-carboxylic acid methylamide (360 mg; 0.82 mmole) was coupled to (2E)-5-(*tert*-butoxycarbonylamino)-5-methyl-2-hexenoic acid using the same coupling procedure as in step D. Removal of the N-terminal Boc group was performed as in step D but at -10 °C. The crude product was purified on a RP-18-Seppak® (5 g; Waters) using a gradient from 0.1%TFA in water/acetonitrile 100/0 to 0.1% TFA in 60/40 water/acetonitrile to afford 306 mg of the title compound as a trifluoroacetate.

<sup>1</sup>H-NMR: δ (MeOH) (selected peaks for major rotamer) 1.30 (s, 3H); 1.31 (a, 3H); 2.10 (AB-syst, 2H); 2.55 (s, 3H); 5.81 (m, 1H).

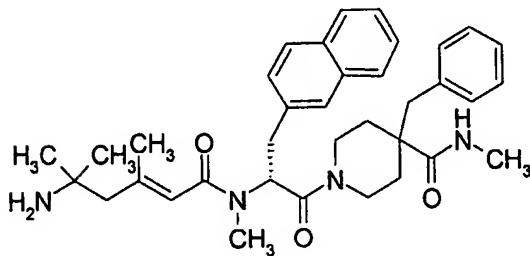
HPLC:  $r_t$  = 31.88 min (A1)

$r_t$  = 33.30 min (B1)

ESMS:  $m/z$  : 569.4 (M+H)<sup>+</sup>.

## Example 2

1-((1R)-2-[N-((2E)-5-Amino-3,5-dimethylhex-2-enoyl)-N-methylamino]-3-(2-naphthyl)propionyl)-4-benzylpiperidine-4-carboxylic acid methylamide



The compound was prepared as in example 1 using (2E)-5-(*tert*-butoxycarbonylamino)-5,3-dimethyl-2-hexenoic acid instead of (2E)-5-(*tert*-butoxycarbonylamino)-5-methyl-2-hexenoic acid in step E

- 5 HPLC:  $r_t = 33.70$  min (A1)  
 $r_t = 34.22$  min (B1)

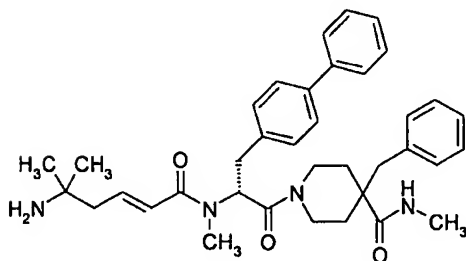
ESMS:  $m/z$  : 583.4 (M+H)<sup>+</sup>.

10

### Example 3

1-{{(2R)-2-[N-((2E)-5-Amino-5-methylhex-2-enoyl)-N-methylamino]-3-(biphenyl-4-yl)propionyl}-4-benzylpiperidine-4-carboxylic acid methylamide

15



This compound was prepared as in example 1 using (2R)-2-*tert*-Butyloxycarbonylamino-N-methyl-3-(4-biphenyl)propionic acid instead of (2R)-2-*tert*-Butyloxycarbonylamino-N-methyl-3-(2-naphthyl)propionic acid in step D.

20

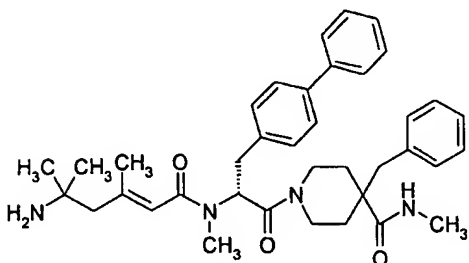
HPLC:  $r_t = 34.53$  min (A1)  
 $r_t = 36.15$  min (B1)

25 ESMS:  $m/z$  : 595.4 (M+H)<sup>+</sup>.

## Example 4

1-((2R)-2-[N-((2E)-5-Amino-3,5-dimethylhex-2-enoyl)-N-methylamino]-3-(biphenyl-4-yl)propionyl)-4-benzylpiperidine-4-carboxylic acid methylamide

5



This compound was prepared as in example 1 using (2R)-2-*tert*-Butyloxycarbonylamino-N-methyl-3-(4-biphenyl)propionic acid instead of (2R)-2-*tert*-Butyloxycarbonylamino-N-methyl-3-(2-naphthyl)propionic acid in step D and using (2E)-5-(*tert*-butyloxycarbonylamino)-5,3-dimethyl-2-hexenoic acid instead of (2E)-5-(*tert*-butyloxycarbonylamino)-5-methyl-2-hexenoic acid in step E.

HPLC:  $r_t = 35.15$  min (A1)  
 $r_t = 36.83$  min (B1)

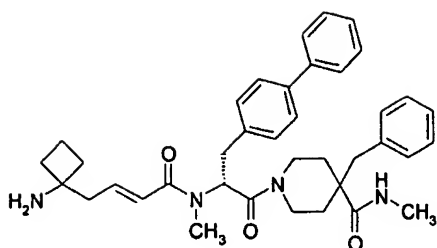
15

ESMS:  $m/z$  : 609.4 (M+H)<sup>+</sup>.

## Example 5

20

1-((2R)-2-[N-((2E)-4-(1-Aminocyclobutyl)but-2-enoyl)-N-methylamino]-3-(biphenyl-4-yl)propionyl)-4-benzylpiperidine-4-carboxylic acid methylamide



This compound was prepared as in example 1 using (2R)-2-*tert*-Butyloxycarbonylamino-N-methyl-3-(4-biphenyl)propionic acid instead of (2R)-2-*tert*-Butyloxycarbonylamino-N-methyl-3-(2-naphthyl)propionic acid in step D and using (2E)-4-(1-(*tert*-  
 5 butyloxycarbonylamino)cyclobutyl)but-2-enoic acid instead of (2E)-5-(*tert*-butyloxycarbonylamino)-5-methyl-2-hexenoic acid in step E.

HPLC:  $r_t = 35.15$  min (A1)

$r_t = 36.68$  min (B1)

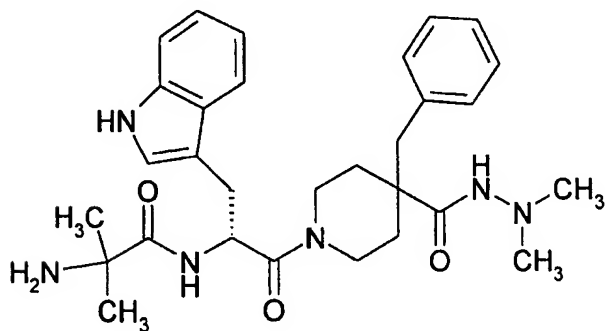
10

ESMS:  $m/z : 607.4 (M+H)^+$ .

#### Example 6

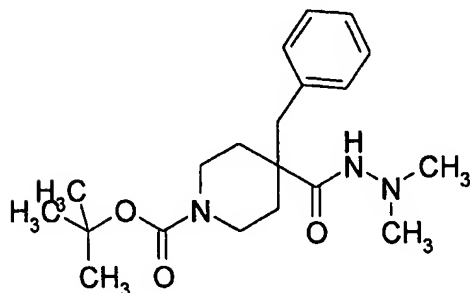
15

2-Amino-N-[(1R)-2-[4-benzyl-4-(N',N'-dimethylhydrazinocarbonyl)piperidin-1-yl]-1-((1H-indol-3-yl)methyl)-2-oxoethyl]-2-methylpropionamide



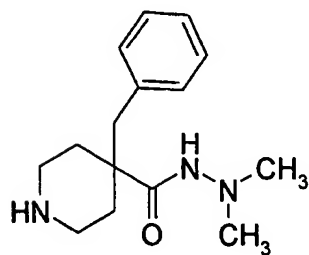
20



4-Benzyl-4-(*N,N'*-dimethylhydrazinocarbonyl)piperidine-1-carboxylic acid *tert*-butyl ester

To a solution of 4-benzylpiperidine-1,4-dicarboxylic acid 1-*tert*-butyl ester (0.75 g, 2.35  
5 mmol) (prepared as in Gilligan *et al* J. Med. Chem. 1994, 364-370 ) in methylene chloride  
(10 ml) was added 1-hydroxy-7-azabenzotriazole (0.32 mg, 2.35 mmol) and 1-ethyl-3-(3-  
dimethylaminopropyl)carbodiimide hydrochloride (0.45 g, 2.35 mmol) and the mixture was  
stirred for 30 min. Then *N,N'*-dimethylhydrazine (0.27 ml, 3.53 mmol) and diisopropylethy-  
lamine (0.52 ml, 3.06 mmol) was added and the mixture was stirred for 2 days. Methylene  
10 chloride (100 ml) was added and the mixture was washed with saturated aqueous sodium  
hydrogencarbonate (20 ml), water (20 ml), dried (MgSO<sub>4</sub>), filtered and concentrated in  
vacuo. The obtained oil was chromatographed on silica (40 g) with heptane/ethyl acetate  
(1:2) to give 0.76 g of 4-benzyl-4-(*N,N'*-dimethylhydrazinocarbonyl)piperidine-1-carboxylic  
acid *tert*-butyl ester as a colorless oil.

15

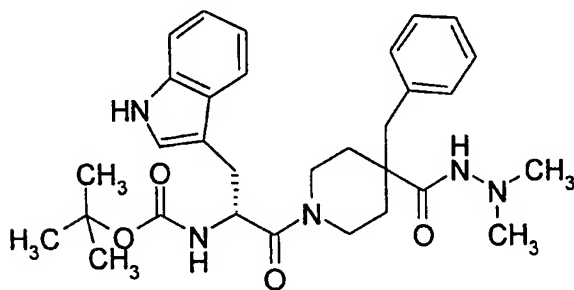
HPLC:  $R_t = 9.66$  min (H8)LC-MS:  $R_t = 9.29$  min,  $m/z = 362.0$  ( $m+1$ )20 4-Benzylpiperidine-4-carboxylic acid *N,N'*-dimethylhydrazide

To a solution of 4-benzyl-4-(*N,N'*-dimethylhydrazinocarbonyl)piperidine-1-carboxylic acid *tert*-butyl ester (0.76 g, 2.02 mmol) in methylene chloride (2 ml) at 0°C was added trifluoroacetic acid (5 ml) and the mixture was stirred for 60 min. The mixture was quenched  
 5 with ethanol (20 ml), concentrated in vacuo and stripped three times with methylene chloride to give 4-benzylpiperidine-4-carboxylic acid *N,N'*-dimethylhydrazide in quantitative yield.

LC-MS:  $R_t$  = 5.64 min,  $m/z$  = 262.0 ( $m+1$ )

10

(2-(4-Benzyl-4-(*N,N'*-dimethylhydrazinocarbonyl)piperidine-1-yl)-1-(1*H*-indole-3-ylmethyl)-2-oxoethyl)carbamic acid *tert*-butyl ester



15

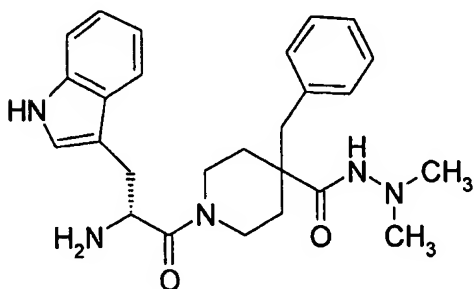
To a solution of 2-*tert*-butoxycarbonylamino-3-(1*H*-indole-3-yl)propionic acid (0.37 g, 1.2 mmol) in methylene chloride (15 ml) and dimethylformamid (5 ml) was added 1-hydroxy-7-azabenzotriazole (0.16 mg, 1.20 mmol) and 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (0.23 g, 1.20 mmol) and the mixture was stirred for 30 min. Then 4-  
 20 benzylpiperidine-4-carboxylic acid *N,N'*-dimethylhydrazide (0.26g, 1.0 mmol) and diisopropylethylamine (0.69 ml, 4.0 mmol) was added and the mixture was stirred overnight. Methylene chloride (100 ml) was added and the mixture was washed with saturated aqueous sodium hydrogencarbonate (20 ml), water (20 ml), dried ( $MgSO_4$ ), filtered and concentrated in vacuo. The obtained oil was chromatographed on silica (40 g) with methylene chloride/(10% ammonia in methanol) (9:1) to give 0.43 g of (2-(4-benzyl-4-(*N,N'*-  
 25 dimethylhydrazinocarbonyl)piperidine-1-yl)-1-(1*H*-indole-3-ylmethyl)-2-oxoethyl)carbamic acid *tert*-butyl ester as a colorless oil.

HPLC:  $R_t = 10.45$  min (H8)

LC-MS:  $R_t = 9.92$  min,  $m/z = 548.2$  ( $m+1$ )

5

1-(2-Amino-3-(1*H*-indol-3-yl)propionyl)-4-benzylpiperidine-4-carboxylic acid *N,N'*-dimethylhydrazide



10

To a solution of (2-(4-benzyl-4-(*N,N'*-dimethylhydrazinocarbonyl)piperidine-1-yl)-1-(1*H*-indole-3-ylmethyl)-2-oxoethyl)carbamic acid *tert*-butyl ester (0.40 g, 0.73 mmol) in methylene chloride (3 ml) at 0°C was added trifluoroacetic acid (3 ml) and the mixture was stirred for 30 min. The mixture was quenched with ethanol (20 ml), concentrated in vacuo and stripped three times with methylene chloride to give 0.63 g of 1-(2-amino-3-(1*H*-indol-3-yl)propionyl)-4-benzylpiperidine-4-carboxylic acid *N,N'*-dimethylhydrazide as a colorless oil.

15

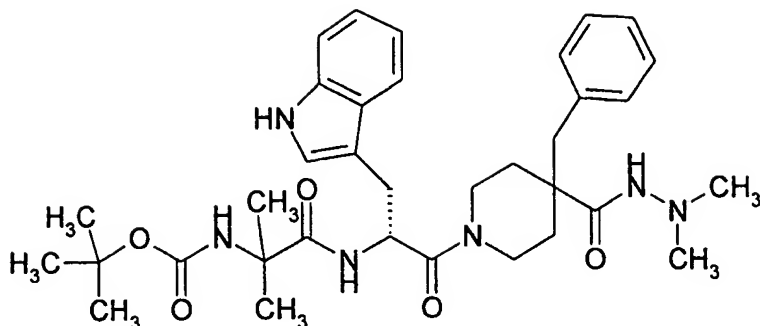
HPLC:  $R_t = 7.52$  min (H8)

LC-MS:  $R_t = 7.61$  min,  $m/z = 448.4$  ( $m+1$ )

20

(1-(2-(4-Benzyl-4-(*N,N'*-dimethylhydrazinocarbonyl)piperidine-1-yl)-1-(1*H*-indol-3-ylmethyl)-2-oxoethyl)carbonyl)-1-methylethyl)carbamic acid *tert*-butyl ester

50

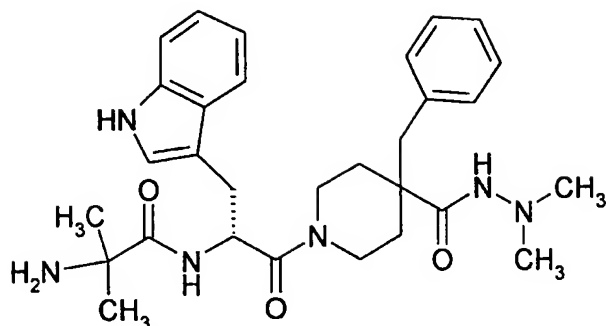


To a solution of 2-*tert*-butoxycarbonylamino-2-methylpropionic acid (0.18 g, 0.88 mmol) in methylene chloride (10 ml) was added 1-hydroxy-7-azabenzotriazole (0.12 mg, 0.88 mmol) and 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (0.12 g, 0.88 mmol) and the mixture was stirred for 30 min. Then 1-(2-amino-3-(1*H*-indol-3-yl)propionyl)-4-benzylpiperidine-4-carboxylic acid *N,N'*-dimethylhydrazide (0.46 g, 0.73 mmol) and diisopropylethylamine (0.50 ml, 2.92 mmol) was added and the mixture was stirred overnight. Methylene chloride (100 ml) was added and the mixture was washed with saturated aqueous sodium hydrogencarbonate (20 ml), water (20 ml), dried (MgSO<sub>4</sub>), filtered and concentrated in vacuo. The obtained oil was chromatographed on silica (40 g) with methylene chloride/(10% ammonia in methanol) (9:1) to give 0.31 g of (1-(2-(4-benzyl-4-(*N,N'*-dimethylhydrazinocarbonyl)piperidin-1-yl)-1-(1*H*-indol-3-yl)methyl)-2-oxoethylcarbamoyl)-1-methylethyl)carbamic acid *tert*-butyl ester as a colorless oil.

15

HPLC:  $R_t$  = 10.25 min (H8)LC-MS:  $R_t$  = 9.66 min,  $m/z$  = 633.2 ( $m+1$ )

20 2-Amino-*N*-[(1*R*)-2-[4-benzyl-4-(*N,N'*-dimethylhydrazinocarbonyl)piperidin-1-yl]-1-((1*H*-indol-3-yl)methyl)-2-oxoethyl]-2-methylpropionamide



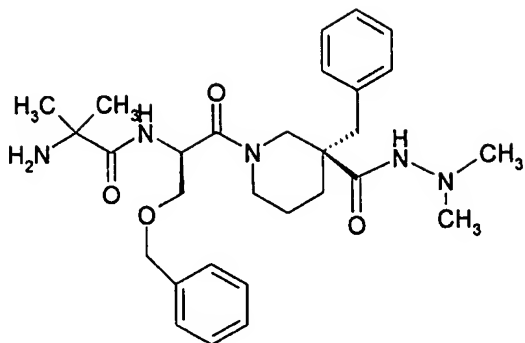
To a solution of (1-(2-(4-benzyl-4-(*N*',*N*'-dimethylhydrazinocarbonyl)piperidine-1-yl)-1-(1*H*-indol-3-ylmethyl)-2-oxoethylcarbamoyl)-1-methylethyl)carbamic acid *tert*-butyl ester (0.29 g, 0.46 mmol) in methylene chloride (3 ml) at 0°C was added trifluoroacetic acid (3 ml) and the mixture was stirred for 30 min. The mixture was quenched with ethanol (20 ml), concentrated in vacuo and stripped three times with methylene chloride to give 0.25 g of 2-amino-*N*-[(1*R*)-2-[4-benzyl-4-(*N*',*N*'-dimethylhydrazinocarbonyl)piperidin-1-yl]-1-((1*H*-indol-3-yl)methyl)-2-oxoethyl]-2-methylpropionamide as a white amorph powder.

HPLC:  $R_t$  = 24.56 min (A1),  $R_t$  = 24.95 min (B1),  $R_t$  = 7.73 min (H8)

LC-MS:  $R_t$  = 7.74 min,  $m/z$  = 533.4 ( $m+1$ )

#### Example 7

2-Amino-*N*-[(1*R*)-2-[(3*R*)-3-benzyl-3-(*N*',*N*'-dimethyl-hydrazinocarbonyl)-piperidin-1-yl]-1-benzyloxymethyl-2-oxo-ethyl]-2-methyl-propionamide

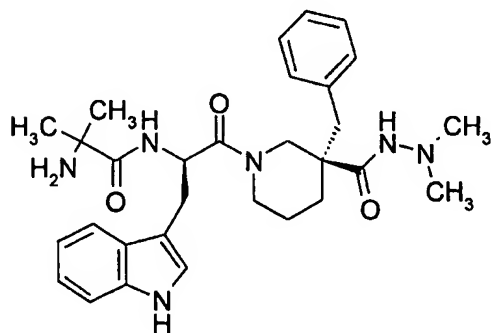


This compound was prepared using the procedure in example 6.

5 ESMS:  $m/z$ : 524.4 (M+H)<sup>+</sup>

#### Example 8

10 2-Amino-*N*-[(1*R*)-2-[(3*R*)-3-benzyl-3-(*N,N'*-dimethylhydrazinocarbonyl)-piperidin-1-yl]-1-((1*H*-indol-3-yl)methyl)-2-oxoethyl]-2-methylpropionamide



15 This compound was prepared using the procedure in example 6.

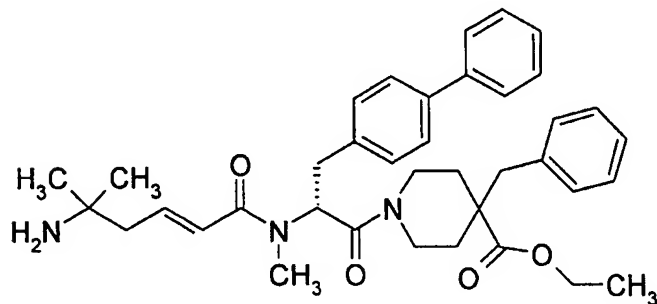
ESMS:  $m/z$ : 533.4 (M+H)<sup>+</sup>

HPLC:  $r_t$ : 27.60 min (A1)

HPLC:  $r_t$ : 26.84 min (B1)

## Example 9

1-[(2R)-2-[N-((2E)-5-Amino-5-methylhex-2-enyl)-N-methylamino]-3-(biphenyl-4-yl)propionyl]-4-benzylpiperidine-4-carboxylic acid ethyl ester



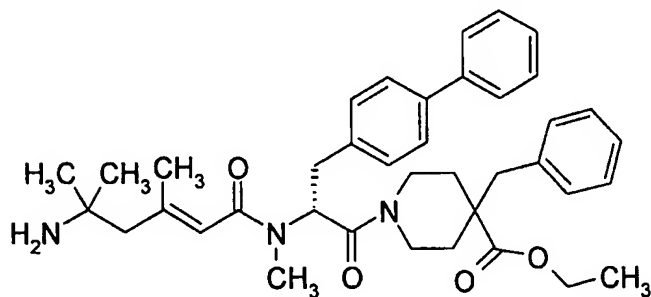
LC-MS: Rt = 12.11 min, m/z: 610.4 (M+H)

HPLC: Rt = 42.075 min (A1)

HPLC: Rt = 44.383 min (B1)

## Example 10

1-[(2R)-2-[N-((2E)-5-Amino-3,5-dimethylhex-2-enyl)-N-methylamino]-3-(biphenyl-4-yl)propionyl]-4-benzylpiperidine-4-carboxylic acid ethyl ester



LC-MS: Rt = 12.36 min, m/z: 624.4 (M+H)

HPLC: Rt = 42.785 min (A1)

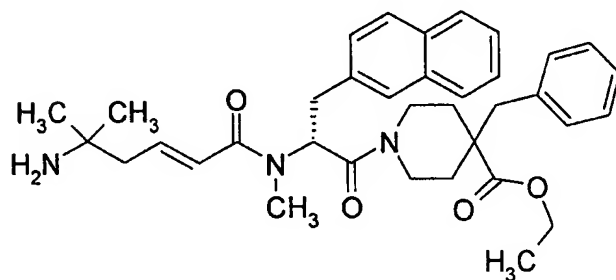
5

HPLC: Rt = 45.148 min (B1)

#### Example 11

10

1-((2R)-2-[N-((2E)-5-Amino-5-methylhex-2-enoyl)-N-methylamino]-3-(2-naphthyl)propionyl)-4-benzylpiperidine-4-carboxylic acid ethyl ester



15

LC-MS: Rt = 11.92 min, m/z: 584.4 (M+H)

HPLC: Rt = 39.893 min (A1)

20

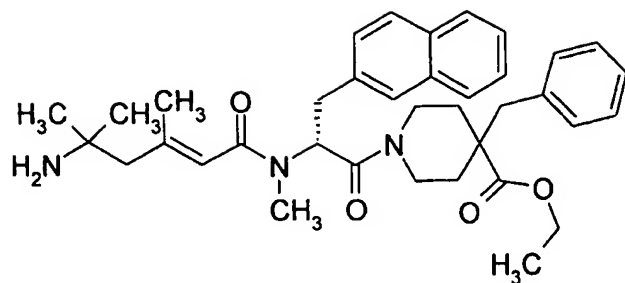
HPLC: Rt = 42.046 min (B1)

#### Example 12

25

1-((2R)-2-[N-((2E)-5-Amino-3,5-dimethylhex-2-enoyl)-N-methylamino]-3-(2-naphthyl)propionyl)-4-benzylpiperidine-4-carboxylic acid ethyl ester





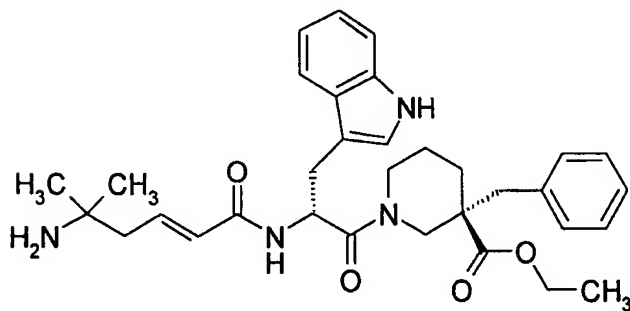
LC-MS: Rt = 12.21 min, m/z: 598.2 (M+H)

5 HPLC: Rt = 40.541 min (A1)

HPLC: Rt = 42.780 min (B1)

10 Example 13

(3S)-1-[(2R)-2-((2E)-5-Amino-5-methylhex-2-enoylamino)-3-(1H-indol-3-yl)propionyl]-3-benzylpiperidine-3-carboxylic acid ethyl ester



15

LC-MS: Rt = 10.07 min, m/z: 559.4 (M+H)

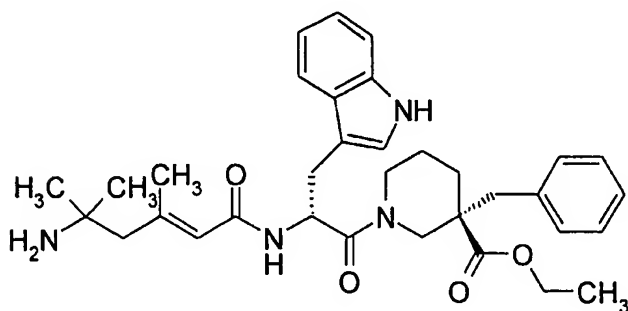
HPLC: Rt = 35.585 min (A1)

20

HPLC: Rt = 37.441 min (B1)

## Example 14

- 5 (3S)-1-[(2R)-2-((2E)-5-Amino-3,5-dimethylhex-2-enoylamino)-3-(1H-indol-3-yl)propionyl]-3-benzylpiperidine-3-carboxylic acid ethyl ester



- 10 LC-MS: Rt = 10.42 min, m/z: 573.2 (M+H)

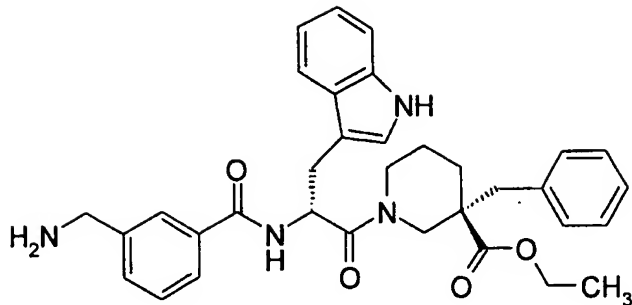
HPLC: Rt = 36.680 min (A1)

HPLC: Rt = 38.563 min (B1)

15

## Example 15

- (3S)-1-[(2R)-2-(3-(Aminomethyl)benzoylamino)-3-(1H-indol-3-yl)propionyl]-3-benzylpiperidine-3-carboxylic acid ethyl ester
- 20



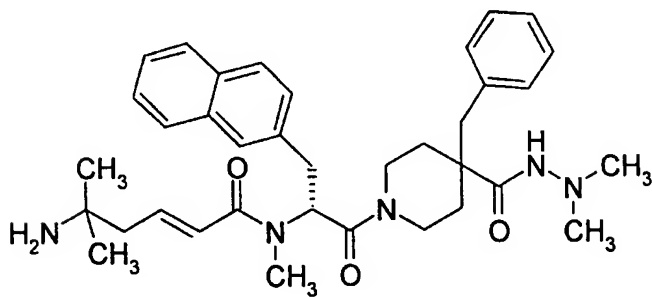
LC-MS: Rt = 10.24 min, m/z: 567.4 (M+H)

5 HPLC: Rt = 36.118 min (A1)

HPLC: Rt = 38.052 min (B1)

10 Example 16

(2E)-5-Amino-5-methylhex-2-enoic acid N-((1R)-2-[4-benzyl-4-(N',N'-dimethylhydrazinocarbonyl)piperidin-1-yl]-1-((2-naphthyl)methyl)-2-oxoethyl)-N-methylamide



15

LC-MS: Rt = 8.82 min, m/z: 598.4 (M+H)

HPLC: Rt = 30.858 min (A1)

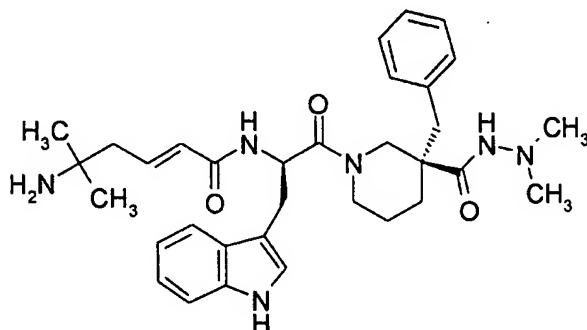
20

HPLC: Rt = 31.198 min (B1)

Example 17

5

(2E)-5-Amino-5-methylhex-2-enoic acid N-[(1R)-2-[3-benzyl-3-(N',N'-dimethylhydrazinocarbonyl)-piperidin-1-yl]-1-((1H-indol-3-yl)methyl)-2-oxoethyl]amide

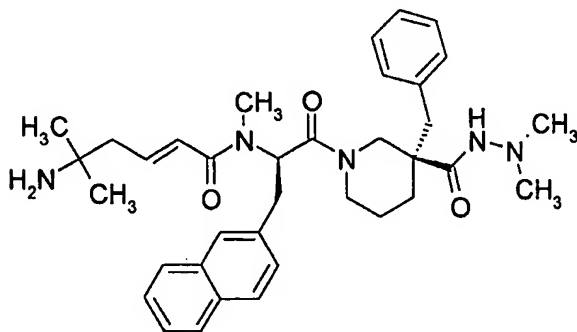


ESMS: m/z : 573.2 (M+H)<sup>+</sup>

10

Example 18

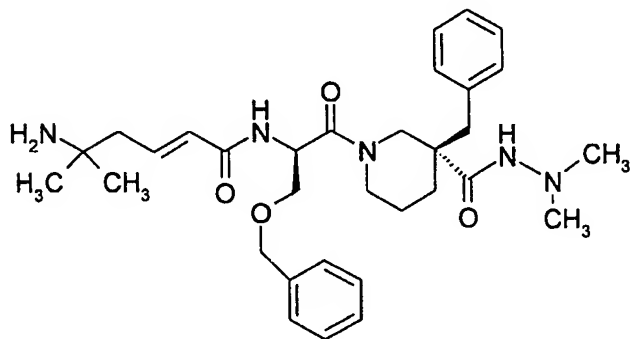
15 (2E)-5-Amino-5-methylhex-2-enoic acid N-[(1R)-2-[3-benzyl-3-(N',N'-dimethylhydrazinocarbonyl)-piperidin-1-yl]-1-((2-naphthyl)methyl)-2-oxoethyl]-N-methylamide



ESMS: m/z : 598.4 (M+H)<sup>+</sup>

## Example 19

(2E)-5-Amino-5-methylhex-2-enoic acid {(1R)-2-[3-benzyl-3-(N',N'-dimethyl-  
5 hydrazinocarbonyl)piperidin-1-yl]-1-(benzyloxymethyl)-2-oxoethyl}amide



LC-MS: Rt = 8.77 min; m/z: 564.2 (M+H)

10

HPLC: Rt = 29.829 min (A1)

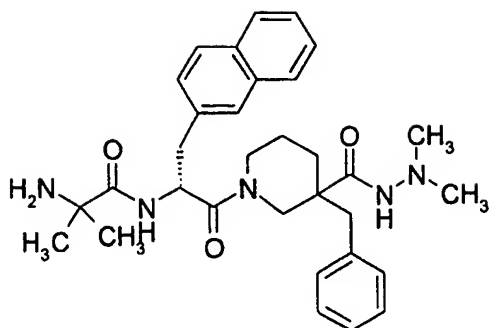
HPLC: Rt = 29.250 min (B1)

15

## Example 20

2-Amino-N-{2-[3-benzyl-3-(N',N'-dimethylhydrazinocarbonyl)piperidin-1-yl]-1-((2-  
naphthyl)methyl)-2-oxo-ethyl}-2-methyl-propionamide

20



LC-MS: Rt = 4.77 min; m/z: 544.4 (M+H)

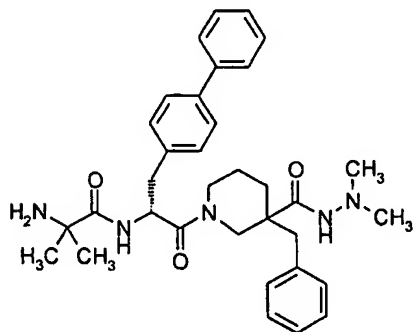
5 HPLC: Rt = 30.900 / 31.586 min (A1)

HPLC: Rt = 30.188 / 30.727 min (B1)

10

#### Example 21

2-Amino-N-((1R)-2-[3-benzyl-3-(N',N'-dimethylhydrazinocarbonyl)piperidin-1-yl]-1-((biphenyl-4-yl)methyl)-2-oxoethyl)-2-methylpropionamide



15

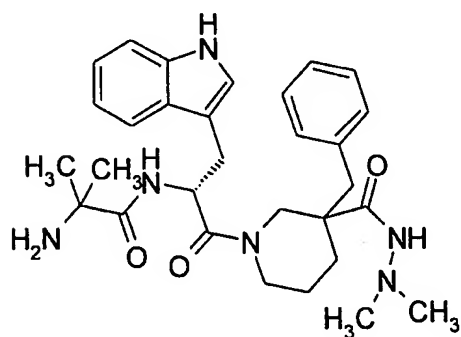
LC-MS: Rt = 4.98 min; m/z: 570.4 (M+H)

HPLC: Rt = 33.839 / 34.313 min (A1)

HPLC: Rt = 33.297 / 33.640 min (B1)

5 Example 22

2-Amino-N-[(1R)-2-[3-benzyl-3-(N',N'-dimethylhydrazinocarbonyl)piperidin-1-yl]-1-[(1H-indol-3-yl)methyl]-2-oxoethyl]-2-methylpropionamide



10

LC-MS: Rt = 4.32 min; m/z: 533.4 (M+H)

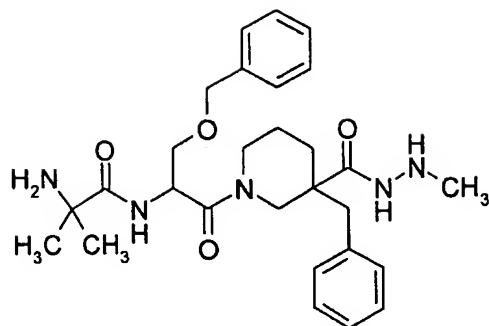
HPLC: Rt = 25.946 / 27.231 min (A1)

15

HPLC: Rt = 25.822 / 26.685 (B1)

20 Example 23

2-Amino-N-[2-[3-benzyl-3-(N'-dimethylhydrazinocarbonyl)piperidin-1-yl]-1-(benzyloxymethyl)-2-oxoethyl]-2-methylpropionamide



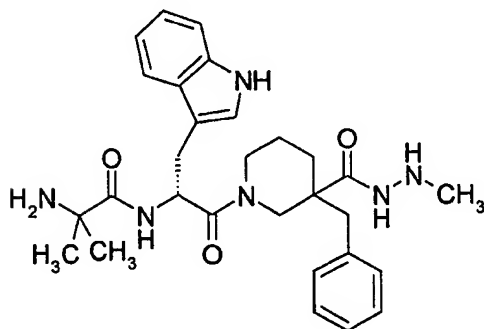
LC-MS: Rt = 4.33 / 4.75 min; m/z: 510.4 (M+H)

5 HPLC: Rt = 30.737 / 30.945 (A1)

HPLC: Rt = 26.809 / 27.307 (B1)

10 Example 24

2-Amino-N-{(1R)-2-[3-benzyl-3-(N',N'-dimethylhydrazinocarbonyl)piperidin-1-yl]-1-(benzyloxymethyl)-2-oxoethyl}-2-methylpropionamide



15

LC-MS: Rt = 4.25 / 5.27 min; m/z: 519.4 (M+H)

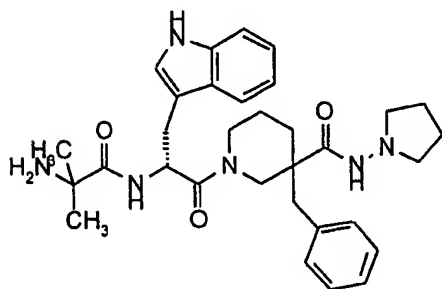
HPLC: Rt = 24.994 min (A1)



HPLC: Rt = 25.742 min (B1)

5 Example 25

1-[(2R)-2-(2-Amino-2-methylpropionylamino)-3-(1-H-indol-3-yl)propionyl]-3-benzylpiperidine-3-carboxylic acid (pyrrolidin-1-yl)amide



10

Mixture of diastereomer

15 Diastereomer I:

LC-MS: Rt = 4.40 min; m/z: 559.4 (M+H)

HPLC: Rt = 26,04 min (A1)

20

HPLC: Rt = 25,79 min (B1)

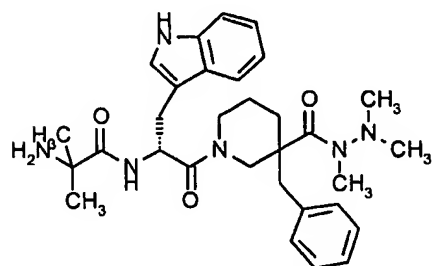
Diastereomer II:

25 HPLC: Rt = 27,38 min (A1)

## Example 26

2-Amino-N-((1R)-2-[3-benzyl-3-(N,N',N'-trimethylhydrazinocarbonyl)piperidin-1-yl]-1-(benzyloxymethyl)-2-oxoethyl)-2-methylpropionamide

5



Mixture of diastereomer

10 Diastereomer I:

LC-MS: Rt = 5,07 min; m/z: 547,4 (M+H)

HPLC: Rt = 32,16 min (A1)

15

Diastereomer II:

LC-MS: Rt = 5,24 min; m/z: 547,4 (M+H)

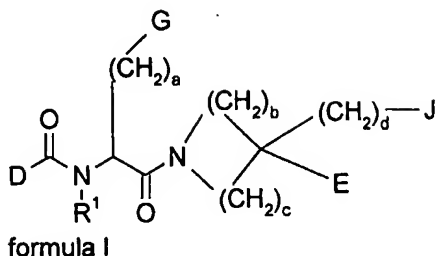
20

HPLC: Rt = 33,60 min (A1)

25 The compounds in examples 9-26 were prepared using the procedures in examples 1-6.

## CLAIMS

1. A compound of the general formula I



wherein

10

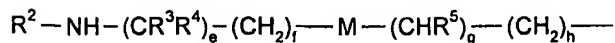
R¹ is hydrogen, or C<sub>1-6</sub>-alkyl optionally substituted with one or more aryl or hetaryl;

a and d are independently of each other 0, 1, 2 or 3;

15

b and c are independently of each other 0, 1, 2, 3, 4 or 5, provided that b + c is 3, 4 or 5,

D is



20

wherein R², R³, R⁴ and R⁵ are independently hydrogen or C<sub>1-6</sub> alkyl optionally substituted with one or more halogen, amino, hydroxyl, aryl or hetaryl; or

R² and R³ or R² and R⁴ or R³ and R⁴ may optionally form -(CH₂)<sub>i</sub>-U-(CH₂)<sub>j</sub>-, wherein i and j are independently 1 or 2 and U is -O-, -S- or a valence bond;

25

h and f are independently 0, 1, 2, or 3;

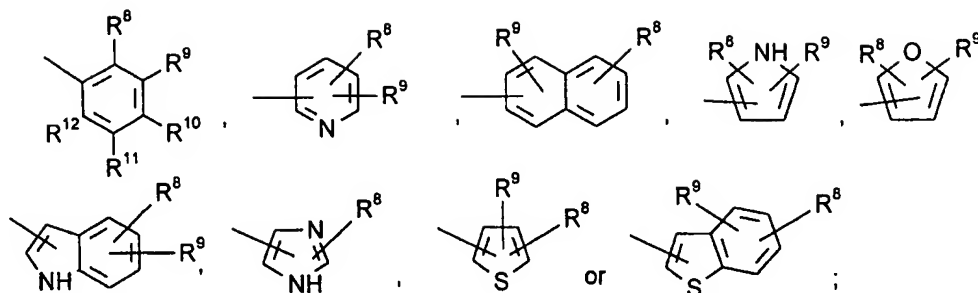
g and e are independently 0 or 1;

M is a valence bond, -CR⁶=CR⁷-, arylene, hetarylene, -O- or -S-;

R⁶ and R⁷ are independently hydrogen, or C<sub>1-6</sub>-alkyl optionally substituted with one or more aryl or hetaryl;

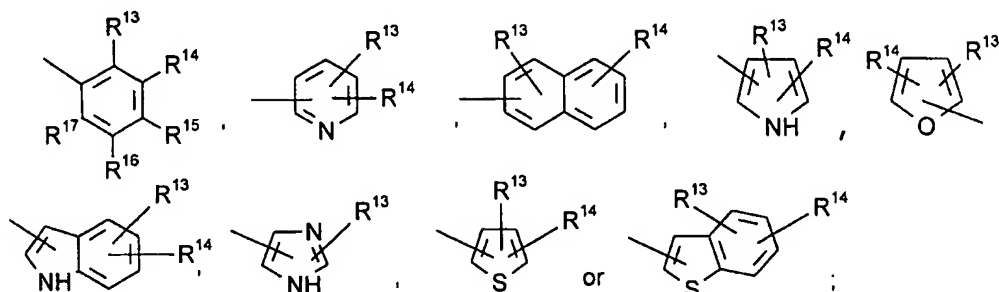
30

G is -O-(CH₂)<sub>k</sub>-R⁸,



J is  $-O-(CH_2)_r-R^{13}$ ,

5



wherein  $R^8, R^9, R^{10}, R^{11}, R^{12}, R^{13}, R^{14}, R^{15}, R^{16}$  and  $R^{17}$  independently of each other are hydrogen, halogen, aryl, hetaryl,  $C_{1-6}$ -alkyl or  $C_{1-6}$ -alkoxy;

10 k and l are independently 0, 1 or 2;

E is  $-\text{CONR}^{18}\text{R}^{19}$ ,  $-\text{COOR}^{19}$ ,  $-(\text{CH}_2)_m-\text{NR}^{18}\text{SO}_2\text{R}^{20}$ ,  $-(\text{CH}_2)_m-\text{NR}^{18}\text{COR}^{20}$ ,  $-(\text{CH}_2)_m-\text{OR}^{19}$ ,  $-(\text{CH}_2)_m-\text{OCOR}^{20}$ ,  $-\text{CH}(\text{R}^{18})\text{R}^{19}$ ,  $-(\text{CH}_2)_m-\text{NR}^{18}-\text{CS}-\text{NR}^{19}\text{R}^{21}$  or  $-(\text{CH}_2)_m-\text{NR}^{18}-\text{CO}-\text{NR}^{19}\text{R}^{21}$ ; or

15

E is  $-\text{CONR}^{22}\text{NR}^{23}\text{R}^{24}$ , wherein  $R^{22}$  is hydrogen,  $C_{1-6}$ -alkyl optionally substituted with one or more aryl or hetaryl, or aryl or hetaryl optionally substituted with one or more  $C_{1-6}$ -alkyl;  $R^{23}$  is  $C_{1-6}$ -alkyl optionally substituted with one or more aryl or hetaryl, or  $C_{1-7}$ -acyl; and  $R^{24}$  is hydrogen,  $C_{1-6}$ -alkyl optionally substituted with one or more aryl or hetaryl; or aryl or hetaryl  
 20 optionally substituted with one or more  $C_{1-6}$ -alkyl; or

$R^{22}$  and  $R^{23}$  together with the nitrogen atoms to which they are attached may form a heterocyclic system optionally substituted with one or more  $C_{1-6}$ -alkyl, halogen, amino, hydroxyl, aryl or hetaryl; or

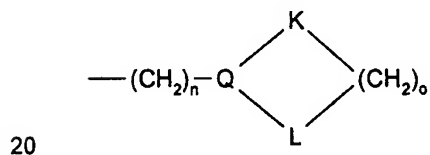
- 5  $R^{22}$  and  $R^{24}$  together with the nitrogen atoms to which they are attached may form a heterocyclic system optionally substituted with one or more  $C_{1-6}$ -alkyl, halogen, amino, hydroxyl, aryl or hetaryl; or

- 10  $R^{23}$  and  $R^{24}$  together with the nitrogen atom to which they are attached may form a heterocyclic system optionally substituted with one or more  $C_{1-6}$ -alkyl, halogen, amino, hydroxyl, aryl or hetaryl;

wherein m is 0, 1, 2 or 3,

- $R^{18}$ ,  $R^{19}$  and  $R^{21}$  independently are hydrogen or  $C_{1-6}$ -alkyl optionally substituted with halogen, -  
 15  $N(R^{25})R^{26}$ , wherein  $R^{25}$  and  $R^{26}$  are independently hydrogen or  $C_{1-6}$  alkyl; hydroxyl,  $C_{1-6}$ -alkoxy,  $C_{1-6}$ -alkoxycarbonyl,  $C_{1-6}$ -alkylcarbonyloxy or aryl;

or  $R^{19}$  is



wherein

Q is  $-CH<$  or  $-N<$ ,

K and L are independently  $-CH_2-$ ,  $-CO-$ ,  $-O-$ ,  $-S-$ ,  $-NR^{27}-$  or a valence bond,

where  $R^{27}$  is hydrogen or  $C_{1-6}$  alkyl;

- 25 n and o are independently 0, 1, 2, 3 or 4;

$R^{20}$  is  $C_{1-6}$  alkyl, aryl or hetaryl;

or a pharmaceutically acceptable salt thereof;

with the proviso that

if M is a valence bond then E is  $-CONR^{22}NR^{23}R^{24}$ .

2. The compound according to claim 1 wherein R<sup>1</sup> is C<sub>1-6</sub>-alkyl.

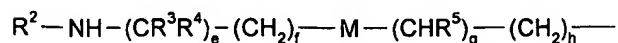
3. The compound according to claims 1 or 2 wherein a is 1.

5 4. The compound according to any one of the preceding claims wherein d is 1.

5. The compound according to any one of the preceding claims wherein b+c is 4.

6. The compound according to any one of the preceding claims wherein D is

10



wherein R<sup>2</sup>, R<sup>3</sup>, R<sup>4</sup> and R<sup>5</sup> are independently hydrogen or C<sub>1-6</sub> alkyl optionally substituted with one or more halogen, amino, hydroxyl, aryl or hetaryl; or

15 R<sup>2</sup> and R<sup>3</sup> or R<sup>2</sup> and R<sup>4</sup> or R<sup>3</sup> and R<sup>4</sup> may optionally form -(CH<sub>2</sub>)<sub>i</sub>-U-(CH<sub>2</sub>)<sub>j</sub>-, wherein i and j are independently 1 or 2 and U is -O-, -S- or a valence bond;

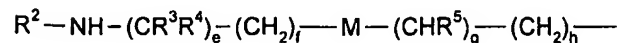
h and f are independently 0, 1, 2, or 3;

g and e are independently 0 or 1;

M is -CR<sup>6</sup>=CR<sup>7</sup>-, arylene, hetarylene, -O- or -S-;

20 R<sup>6</sup> and R<sup>7</sup> are independently hydrogen, or C<sub>1-6</sub>-alkyl.

7. The compound according to any of the claims 1-5 wherein D is



25

wherein R<sup>2</sup>, R<sup>3</sup>, R<sup>4</sup> and R<sup>5</sup> are independently hydrogen or C<sub>1-6</sub> alkyl optionally substituted with one or more halogen, amino, hydroxyl, aryl or hetaryl; or

R<sup>2</sup> and R<sup>3</sup> or R<sup>2</sup> and R<sup>4</sup> or R<sup>3</sup> and R<sup>4</sup> may optionally form -(CH<sub>2</sub>)<sub>i</sub>-U-(CH<sub>2</sub>)<sub>j</sub>-, wherein i and j are independently 1 or 2 and U is -O-, -S- or a valence bond;

30 h and f are independently 0, 1, 2, or 3;

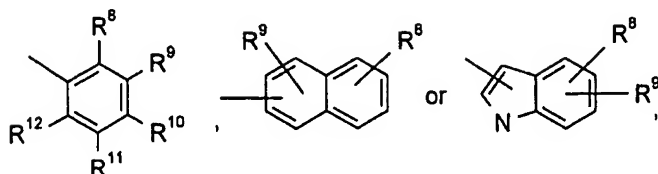
g and e are independently 0 or 1;

M is a valence bond.

8. The compound according to any one of the preceding claims wherein G is



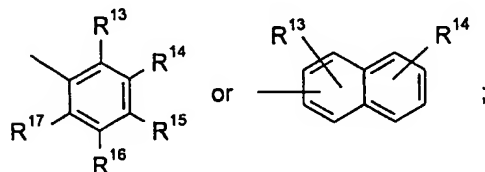
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wherein  $\text{R}^8$ ,  $\text{R}^9$ ,  $\text{R}^{10}$ ,  $\text{R}^{11}$  and  $\text{R}^{12}$  independently of each other are hydrogen, halogen, aryl, hetaryl,  $\text{C}_{1-6}$ -alkyl or  $\text{C}_{1-6}$ -alkoxy;

10 k is 0, 1 or 2.

9. The compound according to any one of the preceding claims wherein J is



wherein  $\text{R}^{13}$ ,  $\text{R}^{14}$ ,  $\text{R}^{15}$ ,  $\text{R}^{16}$  and  $\text{R}^{17}$  independently of each other are hydrogen, halogen, aryl, hetaryl,  $\text{C}_{1-6}$ -alkyl or  $\text{C}_{1-6}$ -alkoxy.

15

10. The compound according to any one of the preceding claims wherein E is  $-\text{CONR}^{18}\text{R}^{19}$ ,  $-\text{COOR}^{19}$  or  $-(\text{CH}_2)_m-\text{OR}^{19}$ , wherein m is 0, 1, 2 or 3,  $\text{R}^{18}$  and  $\text{R}^{19}$  independently are hydrogen or  $\text{C}_{1-6}$ -alkyl optionally substituted by halogen,  $-\text{N}(\text{R}^{25})\text{R}^{26}$  wherein  $\text{R}^{25}$  and  $\text{R}^{26}$  are independently hydrogen or  $\text{C}_{1-6}$  alkyl; hydroxyl,  $\text{C}_{1-6}$ -alkoxy,  $\text{C}_{1-6}$ -alkoxycarbonyl,  $\text{C}_{1-6}$ -alkylcarbonyloxy or aryl.

20

11. The compound according to any of the claims 1-9 wherein E is  $-\text{CONR}^{22}\text{NR}^{23}\text{R}^{24}$ , wherein  $\text{R}^{22}$  is hydrogen,  $\text{C}_{1-6}$ -alkyl optionally substituted with one or more aryl or hetaryl, or aryl or hetaryl optionally substituted with one or more  $\text{C}_{1-6}$ -alkyl;  $\text{R}^{23}$  is  $\text{C}_{1-6}$ -alkyl optionally substituted with one or more aryl or hetaryl, or  $\text{C}_{1-7}$ -acyl; and  $\text{R}^{24}$  is hydrogen,  $\text{C}_{1-6}$ -alkyl optionally substituted with one or more aryl or hetaryl; or aryl or hetaryl optionally substituted with one or more  $\text{C}_{1-6}$ -alkyl; or

25

R<sup>22</sup> and R<sup>23</sup> together with the nitrogen atoms to which they are attached may form a heterocyclic system optionally substituted with one or more C<sub>1-6</sub>-alkyl, halogen, amino, hydroxyl, aryl or hetaryl; or

5

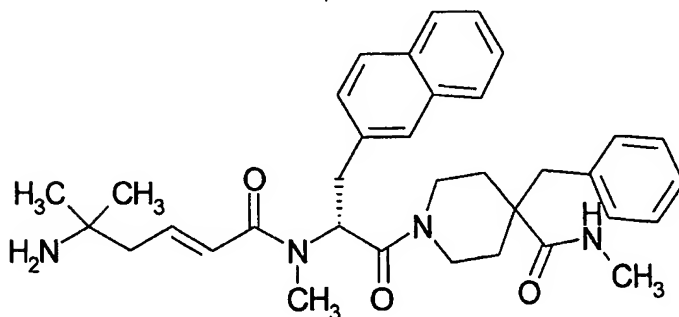
R<sup>22</sup> and R<sup>24</sup> together with the nitrogen atoms to which they are attached may form a heterocyclic system optionally substituted with one or more C<sub>1-6</sub>-alkyl, halogen, amino, hydroxyl, aryl or hetaryl; or

10 R<sup>23</sup> and R<sup>24</sup> together with the nitrogen atom to which they are attached may form a heterocyclic system optionally substituted with one or more C<sub>1-6</sub>-alkyl, halogen, amino, hydroxyl, aryl or hetaryl.

12. The compound according to any one of the preceding claims selected from

15

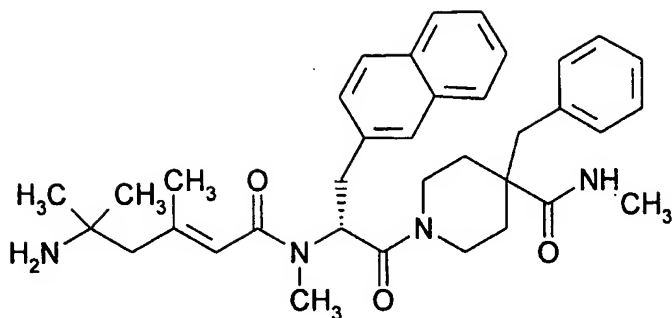
1-[(2R)-2-[N-[(2E)-5-Amino-5-methylhex-2-enoyl]-N-methylamino]-3-(2-naphthyl)propionyl]-4-benzylpiperidine-4-carboxylic acid methylamide



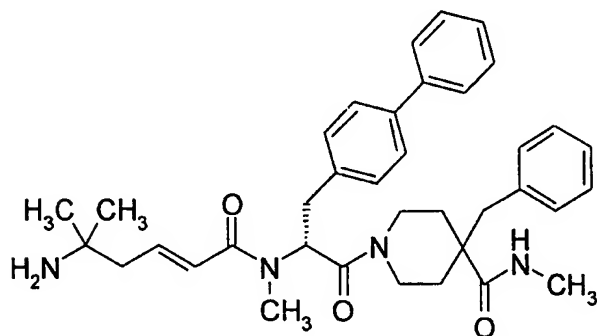
20 1-[(1R)-2-[N-[(2E)-5-Amino-3,5-dimethylhex-2-enoyl]-N-methylamino]-3-(2-naphthyl)propionyl]-4-benzylpiperidine-4-carboxylic acid methylamide



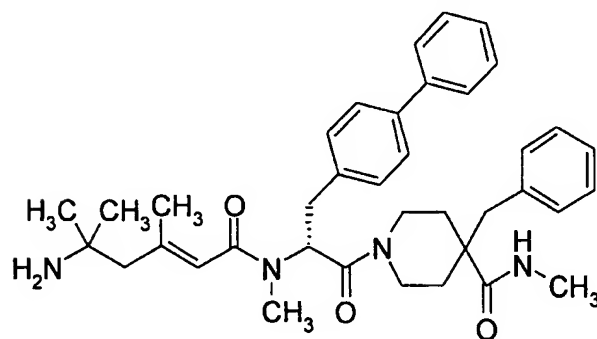
71



1-((2R)-2-[N-((2E)-5-Amino-5-methylhex-2-enoyl)-N-methylamino]-3-(biphenyl-4-yl)propionyl)-4-benzylpiperidine-4-carboxylic acid methylamide

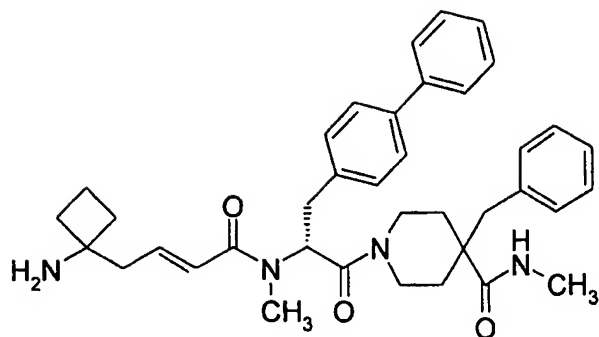


- 5 1-((2R)-2-[N-((2E)-5-Amino-3,5-dimethylhex-2-enoyl)-N-methylamino]-3-(biphenyl-4-yl)propionyl)-4-benzylpiperidine-4-carboxylic acid methylamide



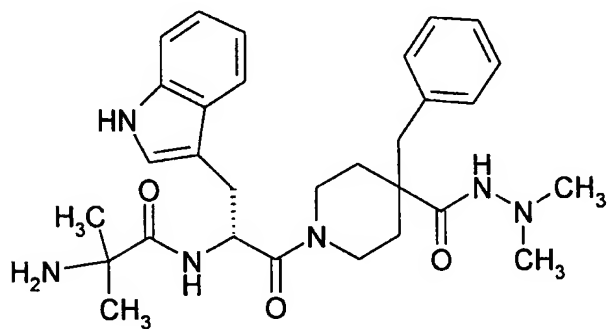
1-((2R)-2-[N-((2E)-4-(1-Aminocyclobutyl)but-2-enoyl)-N-methylamino]-3-(biphenyl-4-yl)propionyl)-4-benzylpiperidine-4-carboxylic acid methylamide

72



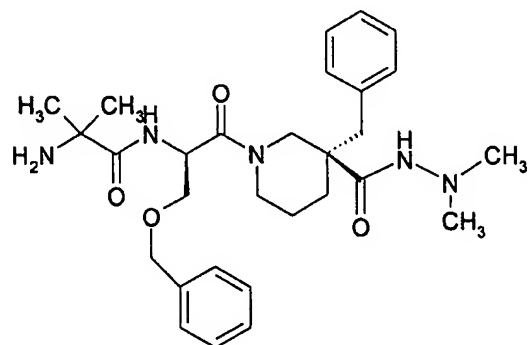
2-Amino-N-[(1R)-2-[4-benzyl-4-(N',N'-dimethylhydrazinocarbonyl)piperidin-1-yl]-1-((1H-indol-3-yl)methyl)-2-oxoethyl]-2-methylpropionamide

5

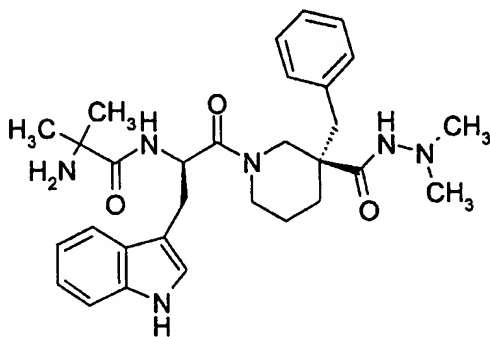


2-Amino-N-[(1R)-2-[(3R)-3-benzyl-3-(N',N'-dimethylhydrazinocarbonyl)piperidin-1-yl]-1-benzyloxymethyl-2-oxoethyl]-2-methylpropionamide

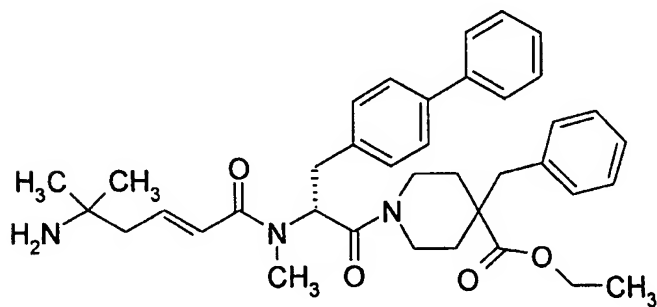
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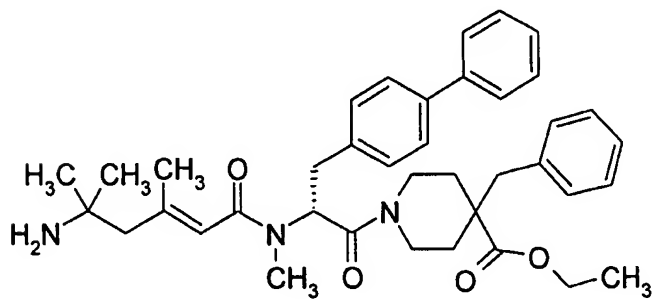
2-Amino-N-[(1R)-2-[(3R)-3-benzyl-3-(*N,N'*-dimethylhydrazinocarbonyl)-piperidin-1-yl]-1-[(1*H*-indol-3-yl)methyl]-2-oxoethyl]-2-methylpropionamide



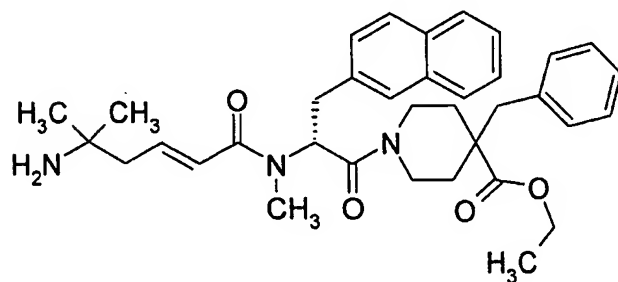
- 5 1-[(2R)-2-[N-[(2E)-5-Amino-5-methylhex-2-enoyl]-N-methylamino]-3-(biphenyl-4-yl)propionyl]-4-benzylpiperidine-4-carboxylic acid ethyl ester



- 10 1-[(2R)-2-[N-[(2E)-5-Amino-3,5-dimethylhex-2-enoyl]-N-methylamino]-3-(biphenyl-4-yl)propionyl]-4-benzylpiperidine-4-carboxylic acid ethyl ester

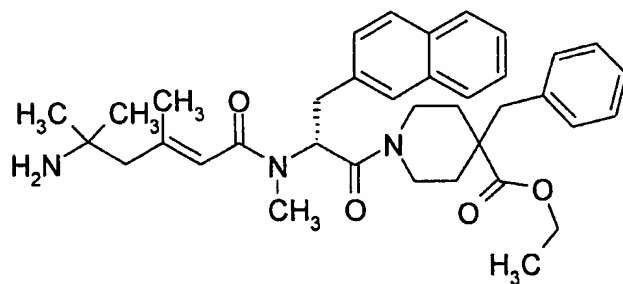


1-[(2R)-2-[N-[(2E)-5-Amino-5-methylhex-2-enoyl]-N-methylamino]-3-(2-naphthyl)propionyl]-4-benzylpiperidine-4-carboxylic acid ethyl ester



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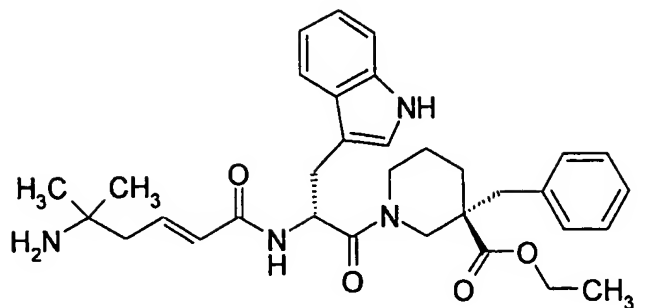
1-[(2R)-2-[N-[(2E)-5-Amino-3,5-dimethylhex-2-enoyl]-N-methylamino]-3-(2-naphthyl)propionyl]-4-benzylpiperidine-4-carboxylic acid ethyl ester



10

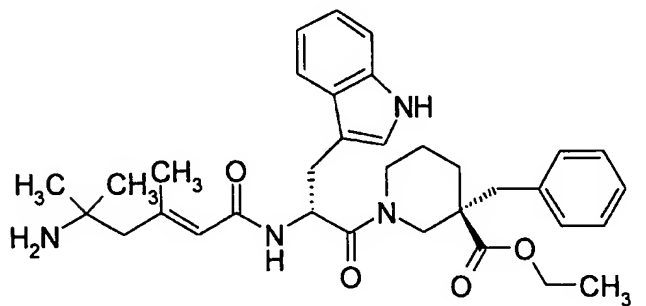
(3S)-1-[(2R)-2-[(2E)-5-Amino-5-methylhex-2-enoylamino]-3-(1H-indol-3-yl)propionyl]-3-benzylpiperidine-3-carboxylic acid ethyl ester

75



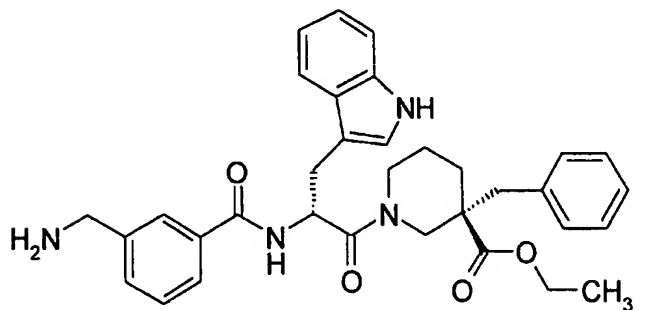
(3S)-1-[(2R)-2-((2E)-5-Amino-3,5-dimethylhex-2-enoylamino)-3-(1H-indol-3-yl)propionyl]-3-benzylpiperidine-3-carboxylic acid ethyl ester

5

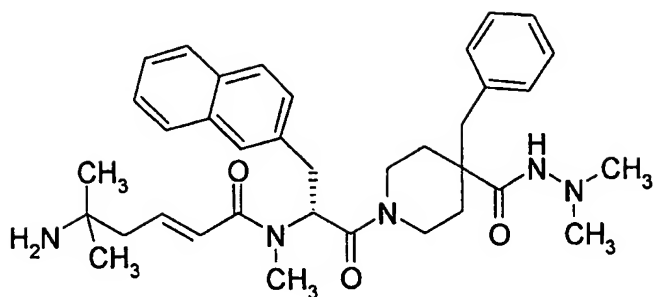


(3S)-1-[(2R)-2-(3-(Aminomethyl)benzoylamino)-3-(1H-indol-3-yl)propionyl]-3-benzylpiperidine-3-carboxylic acid ethyl ester

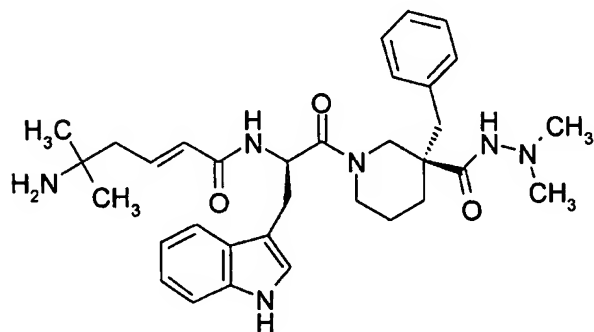
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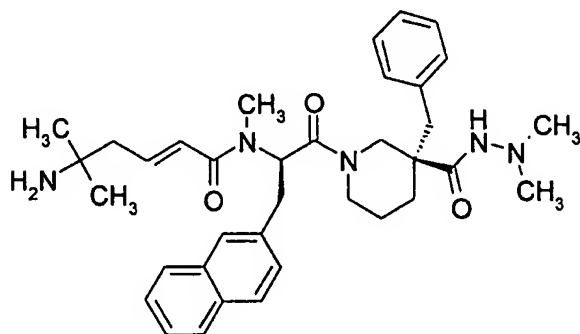
(2E)-5-Amino-5-methylhex-2-enoic acid N-[(1R)-2-[4-benzyl-4-(N',N'-dimethylhydrazinocarbonyl)piperidin-1-yl]-1-[(2-naphthyl)methyl]-2-oxoethyl]-N-methylamide



(2E)-5-Amino-5-methylhex-2-enoic acid N-[(1R)-2-[3-benzyl-3-(N',N'-  
5 dimethylhydrazinocarbonyl)-piperidin-1-yl]-1-((1H-indol-3-yl)methyl)-2-oxoethyl]amide

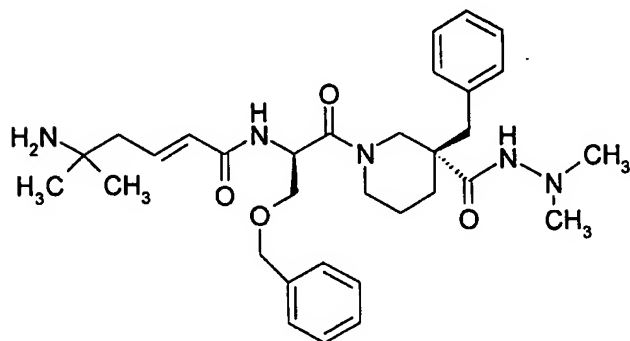


(2E)-5-Amino-5-methylhex-2-enoic acid N-[(1R)-2-[3-benzyl-3-(N',N'-  
10 dimethylhydrazinocarbonyl)-piperidin-1-yl]-1-((2-naphthyl)methyl)-2-oxoethyl]-N-methyl-  
amide



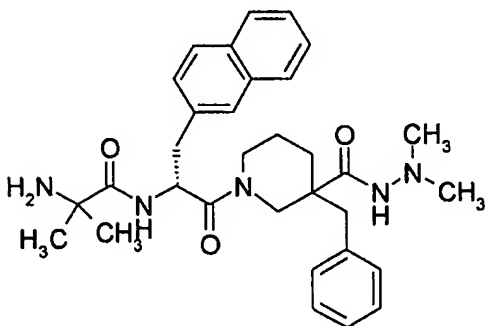
77

(2E)-5-Amino-5-methylhex-2-enoic acid {(1R)-2-[3-benzyl-3-(N',N'-dimethylhydrazinocarbonyl)piperidin-1-yl]-1-(benzyloxymethyl)-2-oxoethyl}amide



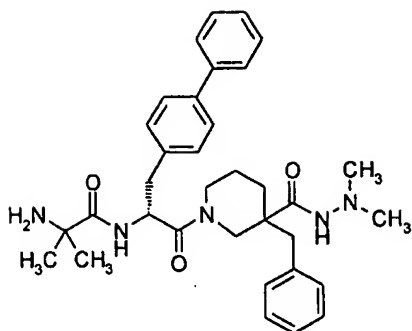
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2-Amino-N-{2-[3-benzyl-3-(N',N'-dimethylhydrazinocarbonyl)piperidin-1-yl]-1-((2-naphthyl)methyl)-2-oxo-ethyl}-2-methyl-propionamide



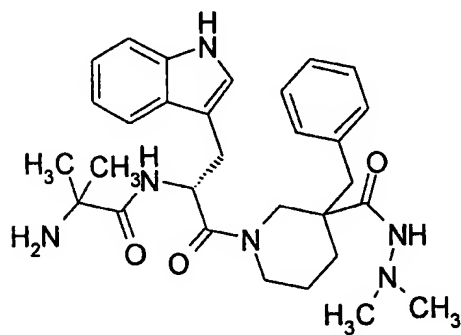
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2-Amino-N-((1R)-2-[3-benzyl-3-(N',N'-dimethylhydrazinocarbonyl)piperidin-1-yl]-1-((biphenyl-4-yl)methyl)-2-oxoethyl)-2-methylpropionamide



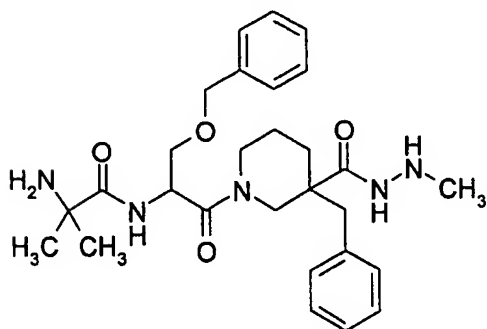
2-Amino-N-((1R)-2-[3-benzyl-3-(N',N'-dimethylhydrazinocarbonyl)piperidin-1-yl]-1-((1H-indol-3-yl)methyl)-2-oxoethyl)-2-methylpropionamide

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2-Amino-N-2-[3-benzyl-3-(N'-dimethylhydrazinocarbonyl)piperidin-1-yl]-1-(benzyloxymethyl)-2-oxoethyl)-2-methylpropionamide

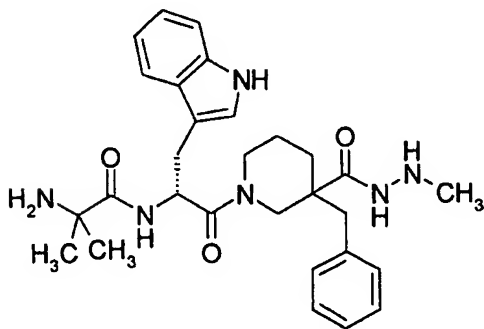
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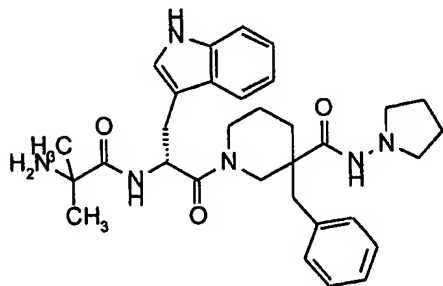
79

2-Amino-N-((1R)-2-[3-benzyl-3-(N',N'-dimethylhydrazinocarbonyl)piperidin-1-yl]-1-(benzyloxymethyl)-2-oxoethyl)-2-methylpropionamide



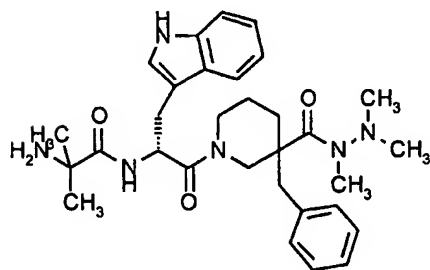
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1-[(2R)-2-(2-Amino-2-methylpropionylamino)-3-(1-H-indol-3-yl)propionyl]-3-benzylpiperidine-3-carboxylic acid (pyrrolidin-1-yl)amide



10

2-Amino-N-((1R)-2-[3-benzyl-3-(N,N',N'-trimethylhydrazinocarbonyl)piperidin-1-yl]-1-(benzyloxymethyl)-2-oxoethyl)-2-methylpropionamide



and pharmaceutically acceptable salts thereof.

13. A pharmaceutical composition comprising, as an active ingredient, a compound according  
5 to any one of the preceding compound claims or a pharmaceutically acceptable salt thereof  
together with a pharmaceutically acceptable carrier or diluent.

14. A method of stimulating the release of growth hormone from the pituitary of a mammal, the  
method comprising administering to said mammal an effective amount of a compound  
10 according to any one of the preceding compound claims or a pharmaceutically acceptable salt  
thereof or of a composition according to any one of the preceding composition claims.

15. Use of a compound according to any one of the preceding compound claims or a  
pharmaceutically acceptable salt thereof for the preparation of a medicament for stimulating  
15 the release of growth hormone from the pituitary of a mammal.

## INTERNATIONAL SEARCH REPORT

International application No.

PCT/DK 99/00260

## A. CLASSIFICATION OF SUBJECT MATTER

IPC6: C07D 211/62, C07D 401/06, A61K 31/445

According to International Patent Classification (IPC) or to both national classification and IPC

## B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC6: C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

SE,DK,FI,NO classes as above

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

## C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 9513069 A1 (MERCK & CO., INC.), 18 May 1995 (18.05.95) --	1-13,15
X	US 5492916 A (GREGORI J. MORRIELLO ET AL), 20 February 1996 (20.02.96) --	1-13,15
X	WO 9635713 A1 (PFIZER, INC.), 14 November 1996 (14.11.96) --	1-13,15
X	US 5721250 A (GREGORI J. MORRIELLO ET AL), 24 February 1998 (24.02.98) --	1-13,15

☒ Further documents are listed in the continuation of Box C.☒ See patent family annex.

\* Special categories of cited documents:

- "A" document defining the general state of the art which is not considered to be of particular relevance
- "E" earlier document but published on or after the international filing date
- "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- "O" document referring to an oral disclosure, use, exhibition or other means
- "P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance: the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance: the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&amp;" document member of the same patent family

Date of the actual completion of the international search

21 July 1999

Date of mailing of the international search report

12-08-1999

Name and mailing address of the ISA:

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Authorized officer

Göran Karlsson/Els  
Telephone No. +46 8 782 25 00

## INTERNATIONAL SEARCH REPORT

International application No.

PCT/DK 99/00260

## C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 9736873 A1 (MERCK & CO., INC.), 9 October 1997 (09.10.97)  --	1-13,15
X	WO 9638471 A1 (PFIZER INC.), 5 December 1996 (05.12.96)  --	1-13,15
X	GB 2308064 A (MERCK & CO INC), 18 June 1997 (18.06.97)  --	1-13,15
X	WO 9816527 A1 (FUJISAWA PHARMACEUTICAL CO., LTD.), 23 April 1998 (23.04.98)  -- -----	1-13,15

# INTERNATIONAL SEARCH REPORT

International application No.  
PCT/DK99/00260

## Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.: 14  
because they relate to subject matter not required to be searched by this Authority, namely:  
**A method for treatment of the human or animal body by therapy,  
see rule 39.1.**
2. ☐ Claims Nos.:  
because they relate to parts of the international application that do not comply with the prescribed requirements to such  
an extent that no meaningful international search can be carried out, specifically:

## Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all  
searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment  
of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report  
covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is  
restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

### Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.  
☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT  
Information on patent family members

01/07/99

International application No.

PCT/DK 99/00260

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9513069 A1	18/05/95	AU 1172995 A	29/05/95
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		EP 0739204 A	30/10/96
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INTERNATIONAL SEARCH REPORT  
Information on patent family members

01/07/99

International application No.

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		AU P0676497 D	00/00/00
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